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PANEL DISCUSSION ON LIPID METABOLISM IN CARDIOVASCULAR DISEASE*

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MODERATOR WILKINSON: At a preliminary meeting, we tried to reconcile our differences of opinion and found that, although we had many points of agreement, we also had many points of disagreement. Perhaps for this reason this particular panel was chosen.

We decided to ask each other questions, unless you have questions to ask us.

We shall start with a subject about which there has been much controversy—the vegetable sterols. There is a difference of opinion here. I shall ask Dr. Kinsell to tell his experience with vegetable sterols.

DR. KINSELL: We have used vegetable sterols only under experimental conditions in the metabolic ward and have not made any studies of them in the last two years. In the phase of the work in which we were trying to determine the common denominator in the cholesterol-lowering effect of a variety of vegetable fats, we gave huge amounts of vegetable sterols, including sitosterol, mixed soy sterols and other forms, up to 60 Gm., which is a great deal for persons on constant diets. In some instances, there were cholesterol-lowering effects, presumably attributable to interference with absorption of either endogenous or exogenous cholesterol, or both, but these effects were rarely of great magnitude. They were unpredictable, and for this reason, we have not continued work in this field.

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MODERATOR WILKINSON: Dr. Stare, would you care to speak on this question?

DR. STARE: No one in our laboratory has had first-hand experience with vegetable sterols.

MODERATOR WILKINSON: Dr. Pollak?

DR. POLLAK: I should like to speak on this question, because I started this whole business.

It is of value to try vegetable sterols. I cannot predict whether anyone will respond or not. Some reports are favorable, others not. From the records, those in favor have it, so far. I should like to ask whether there is anything better to reduce the blood cholesterol level, assuming that you believe it to be desirable.

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: Our own experience is quite limited. The change usually occurs following ingestion of a somewhat substantial amount of vegetable sterol—20 to 30 Gm. per day. There is usually a statistically significant lowering with an average daily ingestion of 15 Gm. of mixed sitosterols. This does not seem very interesting to us. We have stopped this work for the same reason as Dr. Kinsell.

MODERATOR WILKINSON: Dr. Epstein, have you had any experience with this?

DR. EPSTEIN: We have had no experience.

DR. STARE: Dr. Wilkinson, may I make a statement on that? Clinicians around Boston with whom I have talked are not enthusiastic about it. They tend to compare it with resin therapy—a form of treatment that was occasionally used in an attempt to lower the sodium level. You have to take 10, 12, or 15 Gm. of this material with each meal, and also if you have a snack in the afternoon or evening. In other words, it has to be taken every time you eat food. From a practical standpoint and in view of the uncertainty of results and the cost of medication, it is not practical for most patients.

MODERATOR WILKINSON: I might add that in our laboratory we tried every method of administration from mixing it thoroughly with an artificial diet to giving it fifteen, ten or five minutes before the meal. We also gave it in a wafer to be taken every hour while awake.

We had difficulty securing the ingestion of more than 20 or 25 Gm. per day. We found no predictable good results. In some people there seemed to be an initial drop in the cholesterol level that we could not sustain. None of the decreases differed from the cyclic variations seen during a three-year control period in these patients.

I agree with Dr. Stare that it is an impractical way to take medication. On the basis of our results, we believe that not only is it impractical, but not a justifiable way to reduce cholesterol concentration.

MODERATOR WILKINSON: Are there some questions from the audience, or shall we talk among ourselves?

SPEAKER: I should like to ask Dr. Keys whether he believes a deficiency of certain unsaturated essential fatty acids is as important in the pathogenesis of atherosclerosis as an excess of saturated fats?

DR. KEYS: I know of no way in which that question can be answered, at least not in the form in which it was posed.

I presume that we are talking about atherogenesis and not about cholesterol. As far as I know, there is no evidence for anything about atherogenesis in human beings that would be pertinent to that question.

With reference to blood cholesterol concentration, we know that some of the more unsaturated fatty acids are what might be called anticholesterol agents. This is in the sense that they do not induce the increases in cholesterol level that are associated with the ingestion of certain more saturated fats, but there is by no means a regular relationship to the degree of saturation. What this means in terms of atherogenesis in man, we do not know.

MODERATOR WILKINSON: We had agreed not to use the word "anticholesterol." We should like to say, rather, that a hyper- or hypocholesterolemic effect is all that has been noticed with any of these agents. It does not imply a reduction in the endogenous manufacture of cholesterol.

Dr. Kinsell may be able to add something.

DR. KINSELL: The matter of the effect of different kinds of fats represents an area of great interest to us, both fundamentally and clinically. However, I should like to emphasize a statement made by other members of the panel, and which I am sure will be made again, to the effect that in the intact human being, unfortunately, we lack adequate means for short-term evaluation and even less than adequate means for long-term evaluation of what takes place within a blood vessel.

We can measure lipids and all sorts of things in the plasma. The general working hypothesis of almost everyone in this field is that, if one has a choice between a regimen that will produce a low cholesterol level in the blood and one that will produce a high cholesterol level, he takes the regimen that will produce a low level and hopes that this will be good in terms of prevention or progression of the lesion. Much time and work must be devoted to the problem before this is more than a hope.

With that as a baseline, one can say without hedging that the ingestion of a sufficient amount of essential fatty acids (meaning fatty acids of the linoleic or arachidonic acid series, the doubly and quadruply unsaturated fatty acids) under appropriate circumstances will be associated with a decrease in the concentration of blood cholesterol. Moreover, if given in sufficient amount and with appropriate other features in the diet, the decrease in the cholesterol level will be profound. We first noted this in 1951 and have had ample evidence of it since. It has been confirmed by many people. The mechanism is still unclear.

One of the important things for all of us to keep in mind is that cholesterol, which on occasion has been regarded as a very bad "boogy man," is found wherever there is animal life, and as such it undoubtedly has an important physiologic role. Therefore, when approaching this problem, one of the big jobs is not to determine how to get rid of cholesterol, but to determine the normal role of cholesterol and the rules of the game. Then we shall know what to do about the favorable modification of abnormal situations or, better still, the prevention of abnormal situations.

In a chemical sense, there are 3 major lipid materials in the blood. There are other lipids, too, but we shall talk only about these 3. The first is triglyceride,

the glycerol molecule with 3 molecules of fatty acid attached. As far as we know, the make-up of the triglycerides probably varies under normal conditions and bears a significant relationship to the particular diet that is being consumed.

Our working hypothesis is as follows: Triglyceride probably serves as the major source of fuel that keeps the body running throughout the twenty-four hours. This means, then, that a great deal of fatty acid has to be moved around and that the transport of fatty acid is a high-priority situation. Therefore, in an economy noted for overlapping in terms of safety factors, there will be several ways of doing the same thing. The phospholipids also are part of the transport system for fatty acids. For reasons that we do not understand well as yet, one of these fatty acids normally is probably an essential fatty acid.

To run smoothly, the phospholipid must have one essential fatty acid and one nonessential fatty acid. It is the nonessential fatty acid that is constantly being burned and replaced. The essential fatty acid may well be associated with the way the phospholipid fits into certain enzyme systems. As the phospholipids are constantly being broken down and replaced, there has to be a refurbishing of the essential fatty acids, and possibly this is where cholesterol esters are introduced.

This means, then, that the essential fatty acids are just what the name implies. They are vitamins, *i.e.*, they are things that you either get in your diet or you don't get at all, because you cannot make them from other sources. The more saturated acids can be made from the less saturated acids but, once things get below the stage of linoleic acid, nothing can be made above that level. As you know, linoleic has two double bonds.

Since fat and water do not mix, and since fatty acid and these other lipids have to travel around in an essentially aqueous medium, there must be a variety of vehicles to prevent the formation of clumps of fat and consequent fat embolism. The main job of the lipoproteins is to make fat soluble.

MODERATOR WILKINSON: In fairness to our audience, we might point out that when Dr. Kinsell uses the word "essential," it does not imply unanimity of opinion among the investigators in the field. The amount of fat-soluble vitamins is smaller than the amount of fatty acid, saturated or unsaturated, that we are discussing. I do not mean to criticize the term "essential," but I want to point out that many people would prefer to use saturated versus unsaturated rather than essential versus nonessential.

I should like to ask Dr. Stare to talk about this question as he is the only man I know who is illogical enough to cure xanthoma by intravenous feeding of fat.

DR. STARE: Dr. Kinsell used the phrase "under appropriate conditions." This is an important phrase. Under such conditions, one can reduce the serum cholesterol level. These appropriate conditions are, tube feeding, which Dr. Kinsell frequently uses, or formula diets. Formula diets do not consist of meat, potatoes and string beans; they are mixtures of corn oil, sucrose and skimmed-milk powder. Three leaders in that field have been Kinsell, Bevredge in Canada, and Ahrens at the Hospital of the Rockefeller Institute. Under these "appropriate conditions"—the incorporation of large amounts of oil with an unsaturated

fatty acid—it is possible to reduce the concentration of serum cholesterol. Dr. Kinsell has now approached more realistic conditions, in that he has a modified feeding formula; that is, he has a certain type of breakfast and a certain regimented food program. The point I am leading up to is that I know of no evidence which indicates that an appreciable lowering of cholesterol concentration will result if we substitute rather generous amounts of corn or cottonseed oil for the usual amounts of butter, margarine, peanut butter, animal fat or mayonnaise, as an accompaniment of our customary diet of meat, beans, potatoes and grapefruit.

From an experimental point of view, here are some positive results. As Dr. Kinsell showed us this morning, it has been possible in some patients to reduce cholesterol concentration from around 400 mg. to about 270 mg. per 100 cc. In 1 patient, the value was around 260 mg. per 100 cc., and that is quite a reduction. However, I know of no evidence to indicate that, if you add these oils to an ordinary diet in any reasonable quantity, the same thing will take place.

MODERATOR WILKINSON: Is there another question from the audience at this point?

DR. JOLLIFFE: I should like to ask the panel whether there is any way to make a plasticized fat from corn oil, as is done in industry, without destroying its effect in lowering the blood cholesterol level. I know that a fat can be plasticized and remain unsaturated, but can it be plasticized without destroying its effect on the serum cholesterol level?

MODERATOR WILKINSON: I take that to mean, can one hydrogenate up to a point where it is a white fat and not a liquid one. Is that correct?

DR. JOLLIFFE: No. Do you have the *cis* forms and the *trans* forms, or can you leave the unsaturated bonds in these fatty acids, plasticize them, and have them remain almost as unsaturated as before? I have seen no evidence that these fats do not continue to elevate the serum cholesterol level, just as though they were hydrogenated.

MODERATOR WILKINSON: Dr. Stare, would you like to answer that?

DR. STARE: I obviously do not know much about it because I do not understand the term plasticize. The only thing I can say is that I have been told by manufacturers of shortening that they can control the degree of hydrogenation. Little is known about whether or not the isomers that are formed during hydrogenation affect the cholesterol content. As far as I know, the matter has to be limited largely to a discussion of the effect of linoleic acid, much less that of arachidonic acid. There are a few unpublished studies that show that the isomers formed in this reaction have no effect. Dr. Keys mentioned these to me, and perhaps he should tell you about them.

DR. KEYS: I would not want to say much about that question. This is a popular subject to talk about on the basis of no knowledge at all. To my knowledge, at present at least, no one has published or publicly produced evidence that there is any difference whatsoever in the effects of the *cis* and the *trans* forms. That can be stated flatly. Perhaps theoretically *cis* is better than *trans* or vice versa, if you happen to like those configurations but there is no evidence

as yet that these differences are biologically reflected in man. We want to investigate that problem.

I am interested, however, in the question as to whether we are talking about linoleic acid or unsaturation, because they are not necessarily the same thing. Some natural food fats contain considerable linoleic acid. Others have little and may still be more unsaturated than the first. Corn oil is an example of an unsaturated fat that has a fairly large amount of linoleic acid in it. We have made comparisons under rigidly controlled conditions. In the same subjects the regimen was changed from corn oil to sunflower-seed oil (which contains more linoleic acid and is much more unsaturated), or from corn oil to sardine oil (which contains no linoleic acid and little arachidonic acid, but is extremely unsaturated). Under controlled conditions, we invariably found that a change from corn oil to one of these fats caused a rise in the average serum cholesterol level. When people maintained on these fats change to corn oil, the cholesterol level falls.

MODERATOR WILKINSON: Dr. Kinsell, will you tell us what your experience has been?

DR. KINSELL: Going back to the matter of the term "unsaturated" versus "essential"—I personally do not use the term "essential" with any intent to indicate that we must have a pound of this a day, but rather to indicate that it is something which by definition one does not synthesize from other sources. You get it from your food, or you do not get it. It is different from oleic acid, for example, which is a single-bond acid that can be made from all sorts of things, but which is not in the "essential" category. Then there are other saturated or unsaturated substances which we know little about, as some of the other panelists have indicated, and which may not have the same effects as linoleic or arachidonic acid. This is an area where much work remains to be done.

As for relating the effects of an oil or a fat to its content of this so-called essential fat—specifically, linoleic acid—over the years we have carried out studies with safflower-seed oil, cottonseed oil, soybean oil, corn oil and a great variety of oils, and have found that safflower-seed oil per unit of volume will do more than will an equal volume or weight of corn oil. Roughly, this difference in effect is related to the difference in linoleic-acid content.

Recently, we carried out studies with ethyl esters of the fatty acid, that is, compounds with an ethyl radical attached to a simple fatty acid and free, or nearly free, of all other contaminants. In 1 instance, a batch of material of a very high degree of purity produced the same type of change. As far as the data go, these changes appear to be related to the amount of linoleic acid. This probably does not mean that there are not other things in oils which are of importance. In view of all of the interest in essential fatty acids and so forth, I should like to warn against any undue enthusiasm. You will recall that not long ago cholesterol was regarded as a poison to be kept out of the diet at any cost.

We do not wish to have anyone believe that we think that essential fatty acid is the entire answer to the problem of atherosclerosis or to lipid metabolism. That it is an important phase is beyond question.

MODERATOR WILKINSON: I might point out that there is relatively little linoleic acid in mother's milk. Is that not correct?

DR. KINSELL: It is correct that the amount varies with the intake.

MODERATOR WILKINSON: Dr. Keys.

DR. KEYS: In our comparison of 3 fats under rigidly controlled conditions and with metabolic balances, we observed changes in the concentration of serum cholesterol in 26 men. The differences between the levels in the groups fed corn oil, sardine oil and sunflower-seed oil were significant statistically, but whether they were biologically important or not is something else. When the corn oil in a diet was changed to the same amount of sardine oil, the serum cholesterol level rose. In terms of the degree of saturation, sardine oil is much more unsaturated (with a number of 186 in this particular case) than corn oil (with a number of 120).

Similarly, with sunflower-seed oil (our particular batch runs 61 per cent linoleic acid and has the number 140 or 141)—the cholesterol level rose in association with the increase in the intake of linoleic acid and fell with the decrease in intake which occurred in changing from sunflower-seed oil to corn oil.

In experiments with safflower-seed oil (78 per cent linoleic acid) we obtained similar results. If we replaced corn oil with safflower-seed oil, the cholesterol level did not fall. We have done this in both directions.

MODERATOR WILKINSON: I should like to point out that these changes are significant in the statistical sense but, at least as far as the moderator is concerned, they have little significance in the clinical sense.

DR. STARE: It might also be pointed out that the changes Dr. Keys mentioned took place in some 20 people when they were eating meat, potatoes, string beans and grapefruit. He could have shown, as Dr. Kinsell has shown for some years, that if you incorporate these oils into formula diets, or into tube-feeding diets, the changes are much more profound.

DR. KEYS: These diets involve 100 Gm. of experimental fat per day.

MODERATOR WILKINSON: Is there another question from the audience?

DR. KINSELL: With regard to Dr. Wilkinson's statement, may I say again that we would not regard the magnitude of these changes as being significant in a biologic sense.

DR. NATHANSON (from audience): I am a bit flustered. We have had a discussion of acids, and to me it seems that we are discussing something that is present. I, and maybe others, should like to know the opinions of the panelists as to what causes this hypercholesterolemia. We think of androgens and the metabolic activities in the various tissues of the body. However, it would interest us more to have a discussion of the biochemistry of lipid metabolism. I have a certain concept, which may not be totally accepted. I believe that altered lipid metabolism is based upon altered carbohydrate metabolism. As for the biochemistry—in the degradation involved in the transport system and the breakdown of lipids, eventually these compounds have to enter the acetoacetic-acid cycle. In the oxidative phase, there may be some alteration or delay, which accounts for the increased cholesterol content in the blood.

Another point that strikes me is the blanket use of the word cholesterol. Are we to disregard the S_f theory, the S_f-1020, and so forth?

MODERATOR WILKINSON: Yes, I think that we can disregard it.

DR. NATHANSON: We have been taught that theory so long that I should like to know the opinion of the panel today and to have some discussion concerning the chemical basis for hypercholesterolemia, so that we may plan an attack that way.

MODERATOR WILKINSON: I think Dr. Epstein can give us at least one basis for a high versus a low blood cholesterol level. Dr. Epstein.

DR. EPSTEIN: I think I can give at least one reason why serum cholesterol levels may become elevated and one reason why this would seem undesirable. May I also say a few words about atherosclerosis in general because it is this disease primarily rather than the serum cholesterol level, which we wish to control. The concentration of serum cholesterol is determined by multiple factors and so is atherosclerotic disease. In fact, all diseases, including the infectious ones, have multiple causes. As Dudley pointed out twenty years ago, these causes may vary in relative importance, according to space and time. This epidemiologic viewpoint is distinctly relevant to the current discussion. Our approach to this problem depends on the kind of population and the levels of dietary intake. I am convinced that if one compares populations that differ *widely* with regard to fat intake (and possibly in other dietary constituents), they will also differ widely with regard to serum cholesterol levels. The most important single determinant of the amount of atherosclerosis found in such a population may be the quantity of dietary fat. This is Dr. Key's basic theory. To my mind, this is established.

The difficulty comes when we consider a country like the United States where, in general, everybody eats a high fat diet, has a fairly high blood cholesterol level, and has a considerable amount of atherosclerosis. Yet there is good evidence that, within this country, there are marked differences in the frequency of atherosclerosis and probably even differences in blood lipid levels among different population groups. The question arises whether factors other than lipid levels and diet come into play in these situations. In a study we carried out in New York City among clothing workers of Italian and Jewish extraction, we found that Jews had twice as much coronary heart disease, even though their diet differed relatively little from that of the Italians. We were also able to show that this could not be explained solely in terms of the lipid levels among these two groups; other population groups may behave differently.

In this context, it would seem important to decide upon one's aim, when considering dietary or other kind of management of lipid levels. It is becoming obvious that one can change these levels in a number of different ways, more or less successfully—but what magnitude of change would be necessary to affect the prevalence of atherosclerosis?

Let us take 2 population groups, one of which has an average serum cholesterol level of 230 mg., and the other a level of 200 mg. per 100 cc. It is fair to say that people with serum cholesterol levels habitually below 200 mg. per cc. do not have atherosclerosis as often as people with serum cholesterol levels

above 200 mg. It is also fair to say that American populations in general have mean serum cholesterol levels around 230 or 240 mg. per 100 cc. If we assume a standard deviation of 30 mg. per 100 cc., it is obvious that in the population in which the mean level is 230 mg., only 16 per cent of the population will have levels below 200 mg. Consequently, a large proportion (84 per cent) of the population will have potentially atherogenic levels. In a population in which the mean level is 200 mg., as much as half the population will have serum cholesterol levels below 200 mg. Thus, if the concentration of serum cholesterol were the only important determining factor, one might on that basis alone expect a profound difference in the prevalence of coronary heart disease among these 2 population groups whose serum cholesterol levels differ by only 30 mg. per 100 cc. This is the order of magnitude of the change that might be achieved by lowering the dietary fat intake.

Among American population segments whose mean serum cholesterol levels are between 230 and 240 mg. per 100 cc., it may be assumed that a change of 30 mg., or something of that order, will cause appreciable alteration in the prevalence of coronary heart disease. Future epidemiologic studies will solve this particular problem, rather than acute dietary experiments.

MODERATOR WILKINSON: I might summarize this, and then call upon Dr. Stare. It is more or less the consensus of the panel that in discussing changes in blood lipids, the alpha and beta lipoproteins and the concentration of beta-lipoproteins furnished by the S_f values, we are concerned with laboratory theoretic desirable or undesirable changes which will produce atherosclerosis if a diet or a regimen is modified to a considerable degree. Dr. Stare.

DR. STARE: In order to try to answer or comment on Dr. Nathanson's question, I have jotted down a few things which seem to be involved in the causation of atherosclerosis.

There are, certainly, genetic factors. I do not know what we can do about them except to recognize their existence. It has been well established that certain body types favor the development of coronary artery disease. It probably makes little difference how much atherosclerosis one has as long as he does not get a cerebral or coronary thrombosis. The structure of blood vessels has something to do with the development of plaques. As far as I know, this is something that may be on a genetic basis and we cannot do much about it. Let us say, therefore, that genetic factors are involved in this disease, as they probably are in many diseases.

Secondly, estrogens are involved. It has been shown that the level of circulating lipids in the blood stream can be influenced by estrogen therapy. Everyone is well aware that this disease is far more prevalent in the male than in the female, until five or ten years after the menopause when the incidence in the female increases. Experimentally, there are differences among animals. In many cases, the human sex difference is reversed. The female rabbit and the female rat are more susceptible to the experimental production of atherosclerosis than the male. Therefore, estrogens must have something to do with the things that we measure in the blood which supposedly are related to this disease.

The third is diet. Experimentally, half a dozen or more nutrients have been

shown to bear a relationship to the development of atherosclerosis. There also is the question of calories—not only the source, but the amount of calories, because of changes in body weight. In the field of nutrients, fat is being experimented with far more than other nutrients. However, I should like to mention a few of the others that have been studied experimentally.

In our laboratory, we have shown that diets high in sucrose favor the retention of cholesterol in the rat. In other words, there is not only the question of where the cholesterol is coming from and how much is coming, but how much cholesterol is being eliminated. We get rid of cholesterol by the excretion of bile acids. Dr. Portman in our laboratory showed two or three years ago that when the source of carbohydrate in rat diets was changed from sucrose to starch, the animals excreted more bile and got rid of more cholesterol during periods of high starch diets than during periods of high sucrose diets.

One of the usual differences between the diets of primitive groups of people, among whom this disease is relatively rare, and the diets of Americans is the source of carbohydrate. Primitive peoples tend to live off roots. Root vegetables furnish a diet high in starch and low in sucrose. American diets tend to be high in sucrose and lower in starch.

Pyridoxine came into the picture from the original or early studies wherein the late Dr. Reinhart produced a type of arteriosclerosis in monkeys with pyridoxine deficiency. The biochemists have shown that the conversion of linoleic acid to arachidonic acid requires pyridoxine.

In some unpublished studies that my colleague Dr. Waddell has been making at the Massachusetts General Hospital with substantial numbers of people (50 or 60), it was found that administration of huge doses of pyridoxine (about 100 mg. three times a day) caused a marked lowering in the serum cholesterol level. To some extent, this is similar to the report published a few months ago from the Mayo Clinic. They reported the same thing with the use of tremendous amounts of niacin.

Protein metabolism is clearly implicated in the development of atherosclerosis in the experimental animal. We have shown it in the monkey—an animal susceptible to increases in blood cholesterol concentration. If the protein in the diet of the monkey is what is called an "alpha-protein" (derived from soybeans) which is low in organic sulphur, methionine and cystine, and these sulphur compounds are added to the diet, the serum cholesterol level either is not raised or it tends to go down. We have shown the same thing in rats, as published a month ago in the *Journal of Experimental Medicine*. However, these observations on protein in 2 species of experimental animals are not in accord with the observations in man.

In this country, where we have a great deal of coronary artery disease and atherosclerosis, we tend to have an abundance of good-quality protein in our diet. On the other hand, the people of South Africa, Guatemala, Nigeria, Italy and other places, who have a low incidence of this disease, generally have a far lower intake of protein than we do, and it tends to be more from vegetable sources than animal sources as compared with our diet.

Another thing that might be emphasized is that the production of infarction in experimental animals is rare. There are all kinds of reports about the experimental production of atherosclerosis, but relatively few about the production of infarction. In 3 or 4 reports in the literature, the authors claim to have found extensive infarcts in a few of their animals. In our paper in the current issue of the *Journal of Experimental Medicine*, we referred to 1 animal in which there was an extensive infarct; 1 animal among 50 or 60 is not many. I mention this in order to point out that one of the deficiencies of animal studies today is the lack of a procedure or technic to cause infarction.

We have shown in some acute studies in a few people that gaining or losing body weight is a factor that has something to do with the regulation of cholesterol metabolism. Dr. Keys, on the other hand, has shown in nonacute studies with large numbers of people that exercise is a relatively minor matter in regulating cholesterol metabolism. We both agree that it is a factor.

We end up with the fact that atherosclerosis is an important disease, particularly to the American public and to American males. It is a disease subject to experimental attack. It is being attacked, and there have been some advances in the last few years. Involved are the factors of genetics, sex hormones, and diet. An interesting question to ask is whether or not this disease can be prevented. The answer is yes, it can be prevented. What is the evidence? The evidence is the fact that there are millions of people in this world that do not have this disease, which means that it must be preventable!

MODERATOR WILKINSON: Are there any further questions from the floor?

SPEAKER: My question is, what about the thyroid? I should have included that when I mentioned estrogens.

DR. STARE: I should have said that the thyroid hormone has something to do with this, because you can affect the circulating lipid level by the administration of thyroxine, and the level tends to be high in people with hypothyroidism. Experimentally, you can also affect it to a slight degree by administering thyroid hormone.

MODERATOR WILKINSON: Thyroid is wonderful for conditions in which there is a lack of normal hormones. No good clinical evidence has been presented to show that an excess of thyroid is beneficial. Dr. Kinsell, would you like to speak on that?

DR. KINSELL: There is evidence that pharmacologic amounts of thyroid, or related material, will under appropriate circumstances produce a fall in the concentration of blood cholesterol, but I do not think that this is in any way synonymous with the thought that it is a good therapeutic measure, particularly in the group of people who have poor circulatory status initially. If one superimposes an iatrogenic hyperthyroidism, the cure is potentially worse than the disease.

MODERATOR WILKINSON: In 1947 or 1948 at the University of Michigan, we carried out an experiment wherein 6 people, one of whom was myself, became toxic on exogenous thyroid but maintained a normal weight. In none of the 6 persons studied was there a fall in blood cholesterol concentration.

My laboratory has also reported cases of hypercholesterolemia of the familial type, in which there was clinical hyperthyroidism showing no relation to the level of the blood cholesterol. It is true that if a person becomes very thyrotoxic and loses a great deal of weight, the cholesterol level will fall a little.

SPEAKER: I should like to hear the panelists discuss the statistics on blood cholesterol a bit more. For instance, Dr. Epstein noted that at levels of 230 and 200 mg. per 100 cc. or slightly below, there is a statistical difference between 2 population groups. If the difference, say, amounts only to a ratio of 1:2, that may be 100 per cent. What is the relationship when there is a difference of 400 per cent or 1000 per cent—as in Italy where the death rate from coronary artery disease is about one-fourth of ours, or as in Japan where the death rate is only one-tenth of ours. I should like to know more about the situation where there is a different relationship.

MODERATOR WILKINSON: Dr. Epstein, would you like to take that?

DR. EPSTEIN: If there were some way to reduce blood cholesterol levels in this country to the levels that are found, say, in Japan or in various other countries with a low incidence of atherosclerosis, the prevalence of atherosclerotic disease could probably be markedly lowered. As a matter of fact, looking at the data from the cooperative study on lipoproteins, it is evident that there is a marked difference in disease incidence between groups having high and low cholesterol levels. The only trouble in this country is that so few people have low levels.

I think that if there were some way to lower blood cholesterol levels significantly, it would make a striking difference.

DR. POLLAK: There is really no parallelism between high cholesterol levels and atherosclerosis. Let's not fool ourselves. We overemphasize the blood cholesterol level. There is a correlation in familial hypercholesterolemia—a condition in which there is a high incidence of atherosclerosis and complications of the disease, namely, coronary occlusions in young people. By and large, however, the correlation is not clear-cut.

I was happy that Dr. Stare brought up the question of other nutrients and pointed out not only the importance of quantity, but of quality. He mentioned unsaturated fatty acids, methionine, pyridoxine, and so on. I do not believe that everybody in this audience has a lack of unsaturated fatty acids, plant sterols, pyridoxine, nicotinic acid, tocopherol, or methionine. Still, almost every one of us has a considerable degree of atherogenesis, *i.e.*, plaques, in some of our arteries, and some of us here may have had a complication such as infarction. Maybe it is not only what we do *not* eat, but what we eat too much of, that matters. The ratio between unsaturated and saturated fatty acids in our diet may be wrong. A surplus of certain fatty acids may be just as bad as a lack of unsaturated fatty acids.

When we speak of the different factors causing atherosclerosis, we should not overlook the probability that this is not a disease of blood lipids and blood vessels alone, but a disease of the whole body. When a correlation is attempted, it becomes evident that there is an increase of clinically manifest atherosclerosis

with increasing age. There is enzymatic deficiency in aging, and there is liver dysfunction in aging. These may be within what we call physiologic limits, but possibly contributory to the deposit of lipids.

I am not sure that we should attempt to decrease blood cholesterol concentration. Maybe we can prevent the deposition of cholesterol in some other way. Maybe stabilization with albumin, phospholipids, or SH-compounds will provide the answer. It has been shown in experimental animals that the precipitation of lipoprotein molecules can be prevented.

MODERATOR WILKINSON: Dr. Stare has an engagement and must leave at a certain time so I should like to give him a chance to comment at this time.

DR. STARE: Some of our data which have not as yet been published, but which were recently accepted for publication in the *American Journal of Medicine*, show that there is a distinct difference between the cholesterol levels of young males who have infarctions and those who do not have infarctions. My comment on the question that someone raised about the effects of the cholesterol level is that I firmly believe that the level of serum total cholesterol does furnish a measurement of the degree of atherosclerosis. The reason is this: atherosclerosis has been produced experimentally in 6 or 7 species, including the monkey. The only way it has ever been produced is through some mechanism for elevating the concentration of serum lipids, including cholesterol. In the rat studies that we report this month in the *Journal of Experimental Medicine*, the cholesterol levels were in the range of 1000 mg. per 100 cc.—tremendous concentrations that we worked out by a dietary technic to produce atherosclerosis. Why? Because we wanted to do something in the hope that we could produce atherosclerosis. At such concentrations, there is no correlation between the degree of atherosclerosis and the serum cholesterol level, but we are working with levels of 800, 1000 and 1500 mg. per 100 cc.

We have found during the last year or so, in studies that are not yet published, that when we work at much lower cholesterol levels—150, 200 and 225 mg. per 100 cc. (modest elevations compared to the normal range in the rat of 70 to 90 mg. per 100 cc.)—there is clear-cut correlation between the degree of hypercholesterolemia and the extent of the atherosclerotic lesion at necropsy.

I am sure that others have published similar data, so I would say almost without a shadow of a doubt that measurement of the serum total cholesterol level today is the most important single laboratory determination we have for use in trying to evaluate whether a person has, or is developing atherosclerosis.

DR. POLLAK: Would you qualify that and say especially in the lower age group and much less in the older age group?

DR. STARE: Yes, I would.

MODERATOR WILKINSON: It is fair to point out that when Dr. Stare tends to say that this is an index of atherosclerosis, he does not mean in the patient sitting across the table from him. If you choose almost any level of blood cholesterol, or S_f molecules, or blood rhubarb, whichever you want to take, you will find that false positives will far exceed the cases you diagnose correctly.

It is pertinent to mention the long-term studies of Patterson and his group in Western Ontario. They did not find a correlation between the level of blood cholesterol and the degree of atherosclerosis present at necropsy.

It is also of interest that in young persons the average values for blood cholesterol concentration frequently include extremely high levels—as in xanthoma patients, who are much more likely to get atherosclerosis than the person with a modest elevation of cholesterol. Dr. Keys, you probably would like to say something here.

DR. KEYS: I am not quite sure whether we are agreeing or disagreeing about something, and whether this is what the audience wants us to discuss. I agree with Dr. Stare that at present most of us in the field think that determination of the blood cholesterol concentration is the best single measure we now have. If this measurement is carried out in large numbers of people, it can help us to make much better guesses regarding prognosis, as a statistical proposition. At the same time, I emphasize that we cannot make an accurate prognosis or diagnosis with any of these measurements at present.

One difficulty that should be stressed again and again is that we, the American public today, are in general a hypercholesterolemic population already afflicted with atherosclerosis. To try to decide *which* person will be the first to show clinical consequences of this basic fault is rather a foolish proposition, I believe.

MODERATOR WILKINSON: Dr. Kinsell?

DR. KINSELL: Amen, to the last comment and to most of those that preceded it. In masses, fine; but in individuals, we have no "Wassermann" that tells who is going to have a coronary thrombosis or when. May I now or later say something about estrogen?

MODERATOR WILKINSON: At this point, it might be wise to hold that to see if we have a question from the floor.

SPEAKER: As a practicing physician interested in keeping well, I should like to ask whether or not there is any value in such things as choline, methionine and so forth. These drugs are supposed to, and sometimes appear to, reduce the cholesterol level.

The second question is whether or not you can give us anything about the use of iodine in this connection.

MODERATOR WILKINSON: I shall call on the panelists in rotation for this, and take the prerogative of the moderator to say that in my laboratory we do not find choline, methionine or various mixtures of these to be effective. We see no logical reason for their use. We have not used iodides. Dr. Kinsell?

DR. KINSELL: My experience is the same as regards choline and the methionine group. As for the iodides, we have used them but have no idea how to evaluate them. It is our clinical impression that possibly there may be something interesting in this field that warrants careful investigation.

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: With regard to choline, methionine, and the like, we have observed no effect whatsoever in human beings with any of these drugs in their regular

form or with any of the preparations offered to us by pharmaceutical houses. We have not used iodine.

MODERATOR WILKINSON: Dr. Pollak?

DR. POLLAK: Some of these drugs—for instance, iodine—are mild vasodilators. Many aging people have fatty livers, and since the lipotropic substances remove neutral fat (not cholesterol) they may improve liver function and patients may feel better. I don't see much harm, nor any real good, as far as atherosclerosis is concerned. It may be like taking a stimulant.

MODERATOR WILKINSON: Dr. Stare?

DR. STARE: I would not add to any of the comments that have been made. I agree with them.

MODERATOR WILKINSON: Dr. Epstein?

DR. EPSTEIN: No further comment.

MODERATOR WILKINSON: Is there another question from the floor?

SPEAKER: I was interested in what Dr. Pollak said about enzymes. I wonder if a possible reason for an elevated serum cholesterol level might be a deficiency of the enzymes that ordinarily would make the precursors of cholesterol form some more useful compound, but when present in insufficient supply would permit these precursors to turn into cholesterol.

DR. POLLAK: That is my way of thinking about the whole thing. I think that basically there may be a deficiency of some enzyme. I have been hunting for that enzyme (cholesterase) for about fourteen years and I have not yet found it.

MODERATOR WILKINSON: Are there any other questions from the audience?

SPEAKER: I should like to ask the panelists if they know of any work that has been done, or if they have any ideas regarding the effects of environmental factors and perhaps endocrines on the level of cholesterol.

MODERATOR WILKINSON: I am not sure that we understood that, sir. Will you repeat it, please?

SPEAKER: I referred to the effect of strain. Has any work been done to show its effect on cholesterol concentration?

MODERATOR WILKINSON: I think Dr. Keys has a study in progress. I do not know whether he is ready to report on stress and strain at this point, but we shall ask him.

DR. KEYS: As you know, Dr. Wilkinson, some of us have been trying to get at this question of stress and strain for a long time. We have brought psychiatrists, psychosomatists, psychologists, and sociologists in to work with us. The net result is a big zero—mainly, I think, because of lack of good methods. We have no way of measuring it. Thus, the answer is simply that we know nothing about the question of stress and strain. It is unmeasured and unmeasurable at present.

We can say that if modern civilization, telephones, radios, and being run over by automobiles be stressful, we can find plenty of places where these things happen and yet the residents do not have much coronary heart disease. We can also find places where these environmental factors are not operating (as I found last summer and early fall in Finland, a country in which people live simply and

perform much hard physical labor) but where the frequency of coronary heart disease is at least as high as in this country. Therefore, I would say at present that there is no evidence to support the idea that there is a relationship between stress and atherosclerosis, and that on the other hand, there is no definite evidence against it. We are talking in a vacuum most of the time.

MODERATOR WILKINSON: We might at this point ask Dr. Keys whether or not, in Finland, the suicide rate is as high as generally reported throughout the Scandinavian countries. If it is, this might indicate some stress not measured by the simple life.

DR. KEYS: Dr. Wilkinson, we have tried to use various things such as suicide rates and the frequency of diagnosis of neurosis and psychosis, and have found no relationship. Everybody says those things do not have to do with stress and strain.

The highest suicide rate in the world at present is reported to be in Japan, followed by Denmark. What that means, I do not know.

MODERATOR WILKINSON: Are there any other questions?

SPEAKER: My question is about a specific product—Cytellin of Lilly. Can you tell me its value? How does it work, and does it effectively control the level of cholesterol?

MODERATOR WILKINSON: We discussed this question in opening the panel. We thought it better not to name specific products, but we have covered all of the vegetable sterols in rather meager fashion. I think no member of the panel really recommends or uses the material. If I am wrong, I should like the panelists to speak up.

DR. KEYS: Dr. Wilkinson, could we add the point that some of the vegetable sterols, in contradiction to the statements in textbooks, are absorbed and some of them do not appear as cholesterol in the ordinary measurement. Thus, one may have a false sense of security through having a low blood level of cholesterol but a high level of plant sterols. Finally, there is evidence that these materials can appear in the atherosclerotic lesion. Therefore, I do not see where we are getting with this question.

MODERATOR WILKINSON: We might also point out that a week ago last Sunday it was reported by one of the groups at Goldwater Hospital that it is possible to have dihydrocholesterol gallstones in animals fed these substances. Gallstones have not been produced by sitosterol, as far as I know, but by similar substances. I think the subject is far more complex than we have time to go into now, but I do not believe that many laboratories are still enthusiastic about the use of these vegetable sterols. Dr. Pollak, do you want to add something?

DR. POLLAK: The only thing I would like to say is that Cytellin is a sitosterol product. You spoke of the necessity for large doses. If the fat in the diet were restricted to, let us say, 50 per cent and combined with a smaller (50 per cent) dose of sitosterol, perhaps a compromise could be made.

In the first set of patients I reported, I mentioned a case of gallstones in discussion. We do not always have one specific drug for any disease. If nothing else helps to reduce the blood cholesterol level, maybe sitosterol will. It is a question

of trying. If it works, it is all right; if it doesn't, nothing has been lost. As we have seen today, we have nothing much better to offer. Essential fatty acids work in some patients and in others they do not. Nicotinic acid and pyridoxine go down the same drain.

MODERATOR WILKINSON: Have you actually seen sitosterol work in a patient still taking the drug? That is more or less the sense of the question.

Has any of us given his patients sitosterol or the vegetable sterols other than during experimental periods? Is that the question you wanted answered?

SPEAKER: Yes, that is right. I saw it work effectively in hypercholesterolemia, but its effect is wearing off. I wondered if that was your experience, or whether it is a matter of the diet?

MODERATOR WILKINSON: We have had no good results, so we do not use sitosterol in our laboratory any more. Dr. Pollak, how long has any of your patients been taking sitosterol?

DR. POLLAK: The longest is eighteen months.

MODERATOR WILKINSON: Is he still receiving it?

DR. POLLAK: No. I discontinued it. I am not convinced that we have to reduce the blood cholesterol level. Dr. Stare spoke of elevated blood cholesterol levels in younger people with infarction; but what are we trying to diagnose, infarction or atherosclerosis? Some of you may have read 2 papers of mine published not long ago in the *Journal of the American Geriatrics Society*, in which I raised that question. Are we justified in dividing people into goats and sheep according to whether they have had a coronary infarction or not?

MODERATOR WILKINSON: Someone had a question.

SPEAKER: Do the panelists know whether the young Oriental who comes to America and eats an American type of diet has atherosclerosis in later life?

MODERATOR WILKINSON: Dr. Kinsell, you see many young Orientals.

DR. KINSELL: We have quite a few data on young Orientals, most of them second generation. We also have a few data on fairly young Orientals who have recently come to this country and consume something approaching our diet—not identical, because they do not like our diet. There is a significant change in their plasma lipid levels, particularly with reference to cholesterol.

SPEAKER: Thank you.

DR. KEYS: With regard to the Japanese at least, it is evident that a major difference exists between the Japanese in Japan and their relatives from the same part of Japan living in the Hawaiian Islands. During the last two months, we have been able to carry out a cholesterol study on Japanese living in Los Angeles, although there we do not have the necropsy material that we had in Japan and Hawaii.

The average cholesterol concentration for 52 men selected as representative of the business class was compared with that for a Caucasian group at the same time. The 52 Japanese, aged 40 to 49 years, had an average serum cholesterol level of 246.2 mg. per 100 cc. In that community, according to the vital statistics and the records of the Japanese Hospital in Los Angeles, coronary heart disease is the most important and most frequent single cause of death.

MODERATOR WILKINSON: Is there another question?

SPEAKER: I have heard that, in the initial stages of starvation, the blood cholesterol level will often rise. I wonder if that is due to the fact that bile probably was not secreted and cholesterol was therefore retained. Is there any comment on that?

MODERATOR WILKINSON: Dr. Keys wrote a two-volume book on starvation, so I will give it to him.

DR. KEYS: It is not true. In the initial stages of starvation and in total fasting the cholesterol level frequently rises. Our interpretation is that this is associated with the mobilization and transport of lipid for metabolic purposes from the body depots. So far as I know, it has no particular relation to the production, secretion or reabsorption of bile. If you are going to live on the fat of your own body, you still have to try to transport it around as lipid protein and you have to do that by combining it with cholesterol. The liver will make all the cholesterol you want, at any time, or even more than you want.

MODERATOR WILKINSON: Another question?

SPEAKER: I should like to ask Dr. Keys if there are any pathologic changes in the blood vessels of people who are starving. If so, I presume that the lesion would not be the usual atherosclerosis.

DR. KEYS: We have not carried our experiments that far, but we have had the experience of examining material from concentration camps and others have studied material from concentration and prisoner-of-war camps. There is complete unanimity of opinion as to a striking absence of atherosclerosis or any other abnormality that I know of in the blood vessels.

DR. KINSELL: Do you think this would speak for possible reversibility, assuming that a reasonable number of these people might have had atherosclerosis before they got into the starving state?

DR. KEYS: I think, Dr. Kinsell, that that is the only reasonable interpretation you can place upon this observation. We know that under normal circumstances a sizable number of persons have atherosclerosis. The fact that these starved people were uniformly found to be virtually free of atherosclerosis, suggests either that all those who had atherosclerosis were the first ones to die in the prisons, or that there had been some reversal.

DR. POLLAK: May I add one thing. Yesterday afternoon I talked to a pathologist from Germany. He told me about necropsies on prisoners who came from Russian camps. He remarked on the absence of atherosclerosis. Of course, we do not all talk the same language. He added one comment. None of these men had a body weight over 90 pounds.

MODERATOR WILKINSON: It looks as if we can be starved and have reasonable assurance that we won't have atherosclerosis.

DR. KINSELL: May I say one word, Dr. Wilkinson, with regard to a previous statement by Dr. Pollak to the effect that the same kind of variability in results applies to the use of essential fatty acids as applies to the use of sitosterols. I doubt that you meant this. If you did, perhaps you were misinformed. As far

as we know, given a sufficient amount (which may vary with different persons and may be very large) of essential fatty acid such as one of the high linoleic acid-containing fats, any person can have his blood cholesterol level brought within the normal range.

DR. POLLAK: I respect your opinion, but I read the literature and I know that some people disagree with you.

DR. KINSELL: I mean in terms of our own experience over the past six years, which includes controlled and semicontrolled studies in several hundred people.

MODERATOR WILKINSON: This is a matter of how much, not whether. Are there any other questions from the floor?

SPEAKER: Do you have any diet, on the basis of present data, that you would care to recommend to the practicing physician?

MODERATOR WILKINSON: We think that the heterozygous hyperlipemic person is not uncommon, and that, if his fat intake is spaced so that he is able to clear it before he has the next fat load, his blood lipid level can be kept within a theoretically normal range. We also think that there is a real possibility that a person may not be able to clear the fat load from the bloodstream as he grows older. We, more or less arbitrarily, would advise people between 45 and 50 years of age to eat a fat-free breakfast, and anything they want for lunch and dinner. Dr. Kinsell?

DR. KINSELL: We are using 3 diets at present. I think Dr. Wilkinson at this meeting last year made a remark to the effect that there were 2 procedures for lowering the blood cholesterol level. One was caponization by the administration of estrogen and the other was the consumption of some of Kinsell's horrible diets. He implied that he would prefer to have a coronary thrombosis and, in terms of the formula diets and of caponization, we might be inclined to agree.

We have diets now which approach reasonable palatability. The composition of these diets together with our observations will be published in the near future in the *Journal of the American Geriatrics Society*.

MODERATOR WILKINSON: Dr. Keys, have you a diet?

DR. KEYS: The easiest way to get a diet of this sort is to go to some place where the diet is specialized and developed for an entire population. That is why I am sorry that I am not going to be in Italy this spring for the first time in five years.

MODERATOR WILKINSON: Dr. Pollak, have you any diets?

DR. POLLAK: I have no suggestion to make. I agree with what has been said.

MODERATOR WILKINSON: Dr. Epstein?

DR. EPSTEIN: Even though the pathogenesis of the disease is very complex, a cure may be relatively simple. If one could reduce the fat content of the diet in this country, one might make an appreciable dent in the frequency of the condition.

MODERATOR WILKINSON: That is Dr. Epstein's opinion.

SPEAKER: Nothing has been said about the soybean with reference to the Oriental and his diet. I should like to be brought up to date on that.

MODERATOR WILKINSON: The soybean products used in the Oriental diet contain largely protein and practically no fat. The soy meal available to us also contains little fat. I believe Dr. Keys will bear me out in this.

DR. KEYS: That is right; the consumption of soy oil is negligible in Japan. The main form of eating soybeans is soy "curd," which is substantially a fat-free protein.

SPEAKER: Should we recommend soybean for use in America?

DR. KEYS: Not I, after much experience trying to put this across as a war measure in the feeding of soldiers.

SPEAKER: Can you say anything about lecithin and phospholipids in this connection?

MODERATOR WILKINSON: The experience in our laboratory with lecithin has been about the same as that with choline and methionine.

SPEAKER: I should like to ask whether or not any studies have been made comparing any sizable group of vegetarians in this country with ordinary people on ordinary diets?

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: There are not many true vegetarians. Dr. Stare has worked with vegetarians in this country. I think most of them consume milk and milk products and otherwise are not proper vegetarians. There has been a study here in the United States and another in the Netherlands, but I think they are not in full agreement.

MODERATOR WILKINSON: There is quite a group in Southern California in a Medical School—the College of Medical Evangelists. The whole principle of the Seventh Day Adventists is vegetarianism, but it has been implied that there are degrees of vegetarianism.

DR. KINSELL: I had a classmate in medical school who was a vegetarian, but this meant only to the exclusion of rare beefsteak.

MODERATOR WILKINSON: Thank you.

EFFECT OF AGE ON PERIPHERAL VIBRATORY PERCEPTION

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The impairment of peripheral vibratory perception with advancing age is well known. This was originally assessed with a tuning fork (1, 2); latterly more quantitative techniques have been employed using electrical vibrometers (3–8). When studying the effect of age on vibratory perception, it is necessary to exclude all other known factors which may affect this measurement. Although reports in the literature have stated that the subjects tested were free of such factors, insufficient emphasis has been placed on the selection of subjects with completely normal extremities. The present study, therefore, was undertaken to measure peripheral vibratory perception in such a group of aging persons.

An electrical vibrometer was designed which had a frequency of 125 cycles per second. The amplitude of vibration was varied by altering the voltage applied to the vibrator, which consisted of an electromagnetic recording head carrying a blunt needle 1 inch long. The vibratory perception threshold was read in arbitrary "vibration units", 100 units being the maximum obtainable from the machine. (See Appendix for technical description and diagram of the vibrometer).

SUBJECTS

One hundred normal men were studied, ranging in age from 22 to 85 years. These were selected on the basis of history, physical examination, oscillometry and neurologic examination, and were considered to have completely normal extremities. Blood sugar determinations were performed on all of the older men, both fasting and after a meal. Results of serologic tests for syphilis were negative in all cases. None of the subjects had anemia. Particular care was taken to rule out the following: pernicious anemia, diabetes mellitus, peripheral neuritis, peripheral nerve injuries, other neurologic and psychiatric disorders, syphilis, vitamin deficiencies, and peripheral occlusive vascular disease of all types.

METHODS

Vibratory perception thresholds were measured in the hands and feet. For measurement in the hand, the subject was seated comfortably at a table with the hand resting on a slotted board through which the vibrator protruded. The index and fifth fingers were measured, the mid-point of the palmar aspect of the distal phalanx being applied to the vibrator. For measurement in the lower extremity, the foot was rested on a chair, and the vibrator was applied to the mid-point of the plantar surface of the distal phalanx of the big toe. In all cases, the purpose

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of the test was clearly explained and sample vibrations were demonstrated to the subject.

The vibrator was applied to the test point at zero voltage; the voltage was then gradually increased until the subject indicated that he perceived the vibration. This was repeated at least three times at each site. When all the determinations

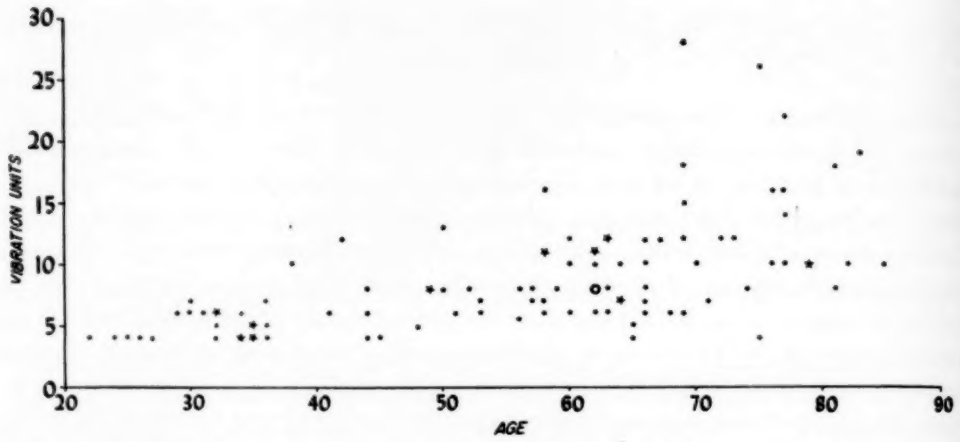

FIG. 1. *Vibratory perception threshold of right index finger.* A single subject is represented by a small star, 2 subjects at the same point by a large star, and 3 by an enclosed star.

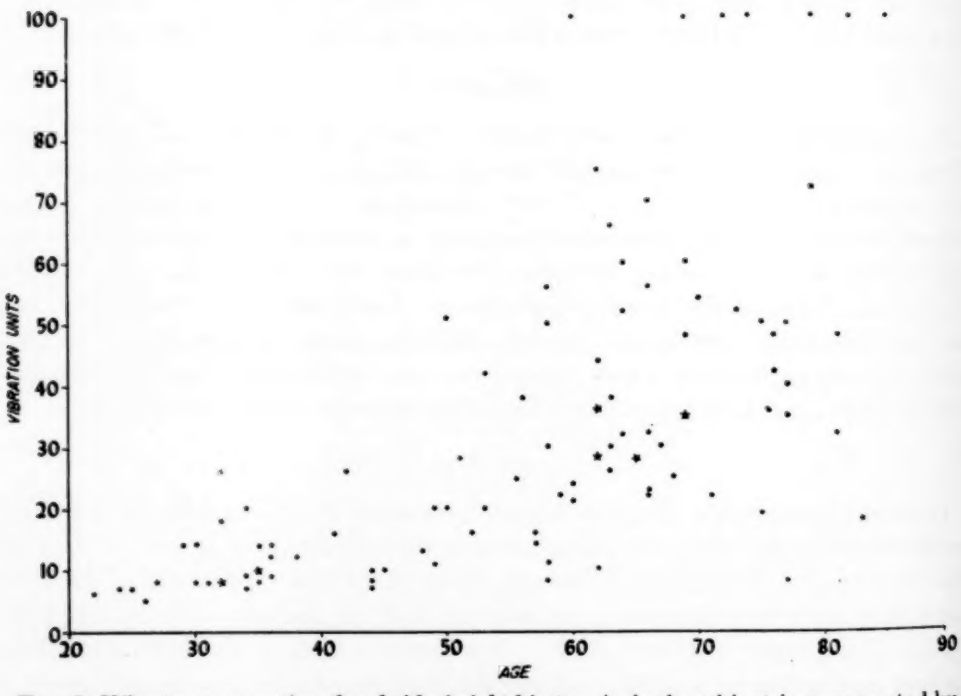

FIG. 2. *Vibratory perception threshold of right big toe.* A single subject is represented by a small star, and 2 subjects at the same point by a large star.

were in good agreement, their mean was taken to be the vibratory perception threshold for that site.

RESULTS

When the results of the test for each site were plotted against age on ordinary graph paper, the points did not form a straight line but appeared to fall along a simple curve—the perception threshold increasing with age. Figures 1 and 2 are representative graphs. When the results were plotted semi-logarithmically using the logarithms of the results plotted against age, the points appeared to fall along a straight line despite great individual variations—the vibratory perception thresholds increasing logarithmically with age at all sites tested. Representative graphs are shown in Figures 3 and 4. The lines of best fit for the 6 sites tested are shown in Figure 5.

There was no significant difference between the perception thresholds at corresponding sites on the two sides of the body (Table 1; Figs. 6, 7 and 8). Statistical confirmation of this observation with reference to the toes is presented in Table 1. The data on the fingers (not shown) were similar for all 4 digits in each age group. The increase in vibratory perception threshold with age was more marked in the toes, 9 of the subjects over 60 years of age being unable to perceive any vibration in either right or left toes. This result was assigned a value of 100 vibration units (the maximum for the instrument).

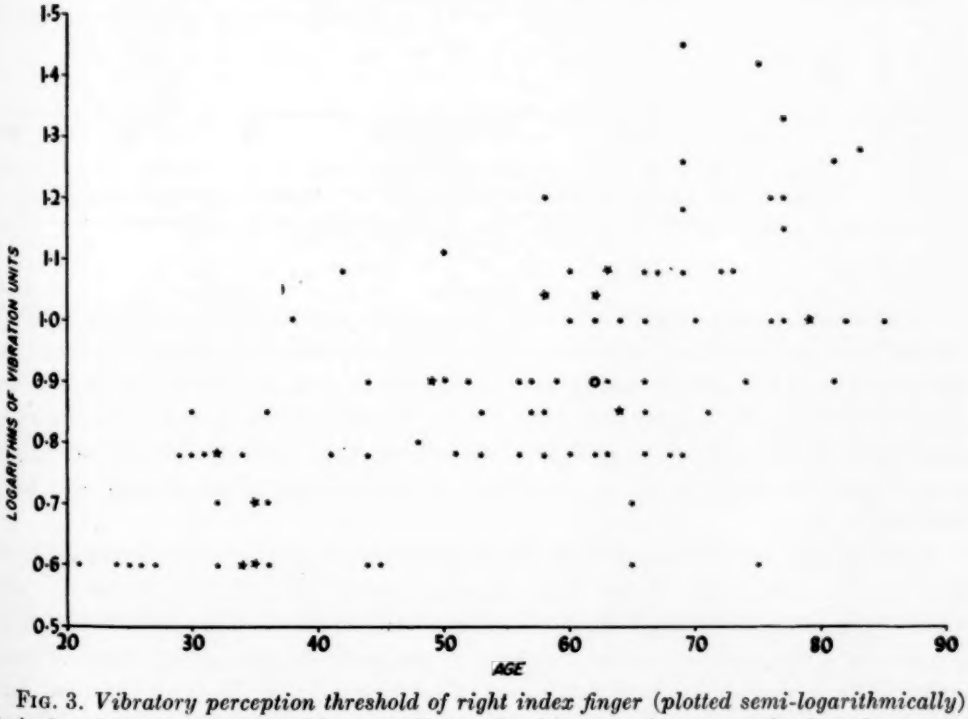

FIG. 3. *Vibratory perception threshold of right index finger (plotted semi-logarithmically).* A single subject is represented by a small star, 2 subjects at the same point by a large star, and 3 by an enclosed star.

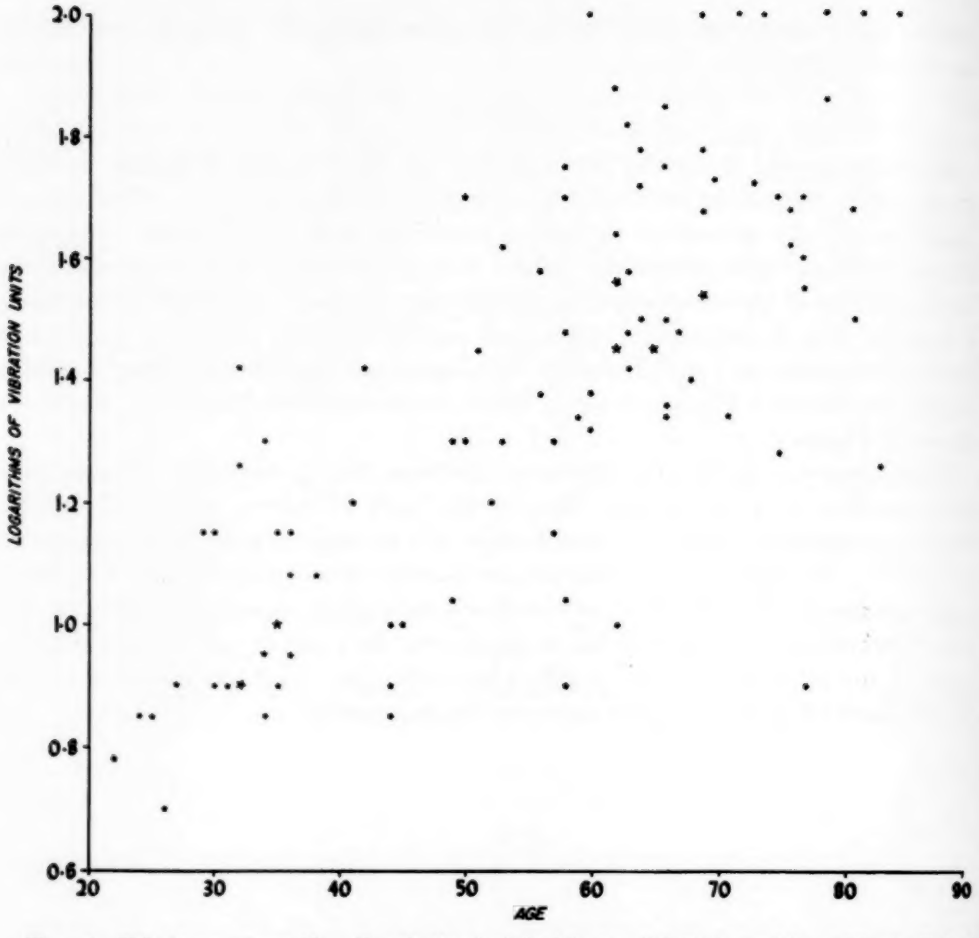

FIG. 4. *Vibratory perception threshold of right big toe (plotted semi-logarithmically).* A single subject is represented by a small star, and 2 subjects at the same point by a large star.

Comparison of the fingers with the toes of the corresponding side revealed a statistically significant difference in vibratory perception thresholds, except for the left side in the 20–29 age group (Table 2). It was interesting that the age groups involving the largest numbers of subjects showed the greatest statistically significant differences. It is probable, therefore, that had the 20–29 age group been larger, the differences in vibratory perception thresholds would also have been significant.

A few exceptions to the general trend were noted in the data. Several of the men less than 60 years of age had vibratory perception thresholds at one site which were excessively high when compared with those of other men in the same age group. These subjects were carefully reassessed but no explanation for these isolated high thresholds was apparent. Conversely, one 75-year-old man had vibratory perception thresholds at all 6 sites which resembled those found in the youngest age group tested.

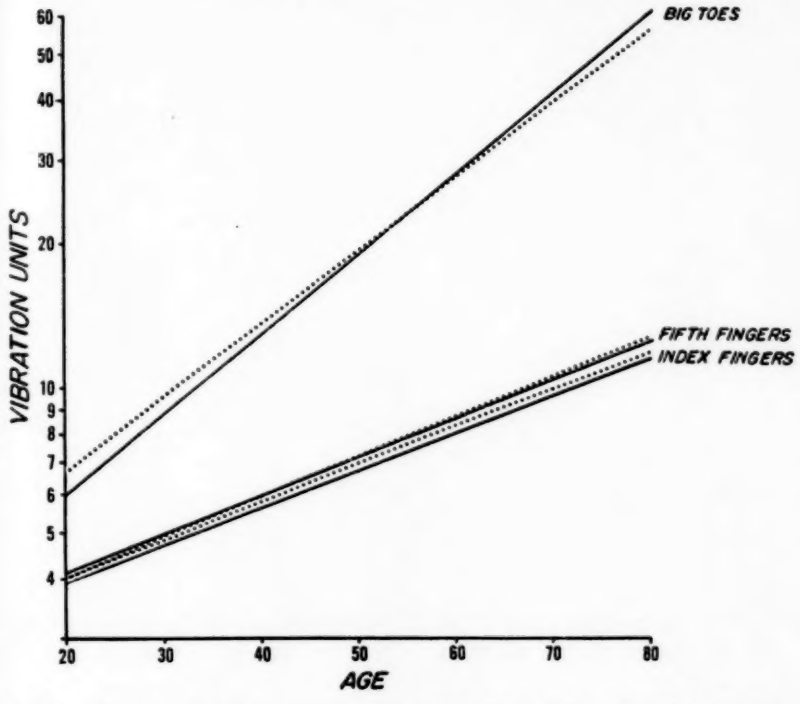

FIG. 5. *Lines of best fit for vibratory perception thresholds.* The right side is represented by solid lines and the left by dotted lines.

TABLE 1

Comparison of Vibratory Perception Thresholds (vibration units) in Right and Left Fingers and Toes

(Means and Standard Errors)

Age of Subject (yrs.)	Index Fingers		Fifth Fingers		Big Toes	
	Right	Left	Right	Left	Right	Left
20–29	4.3 ± 0.3	4.5 ± 0.3	4.6 ± 0.5	4.3 ± 0.2	7.8 ± 1.3	9.1 ± 2.8
P					0.7 > p > 0.6	
30–39	5.4 ± 0.4	4.2 ± 0.4	5.3 ± 0.3	5.2 ± 0.3	11.9 ± 1.2	12.9 ± 1.5
P					0.7 > p > 0.6	
40–49	6.7 ± 0.8	6.2 ± 0.5	6.5 ± 0.7	6.6 ± 0.7	13.4 ± 2.1	13.7 ± 2.0
P					p > 0.9	
50–59	8.5 ± 0.7	9.0 ± 0.9	7.8 ± 0.6	10.2 ± 1.1	27.8 ± 3.9	23.3 ± 3.7
P					0.5 > p > 0.4	
60–69	9.7 ± 0.8	8.9 ± 0.7	10.0 ± 0.6	9.1 ± 0.6	41.8 ± 4.0	41.3 ± 3.0
P					p > 0.9	
70–79	12.4 ± 1.6	12.1 ± 1.4	14.8 ± 2.5	14.6 ± 2.5	52.8 ± 7.5	57.6 ± 7.7
P					0.7 > p > 0.6	
Over 80	13.0 ± 2.3	12.8 ± 1.7	13.6 ± 1.7	12.8 ± 1.4	59.6 ± 17.1	74.4 ± 14.6
P					0.6 > p > 0.5	

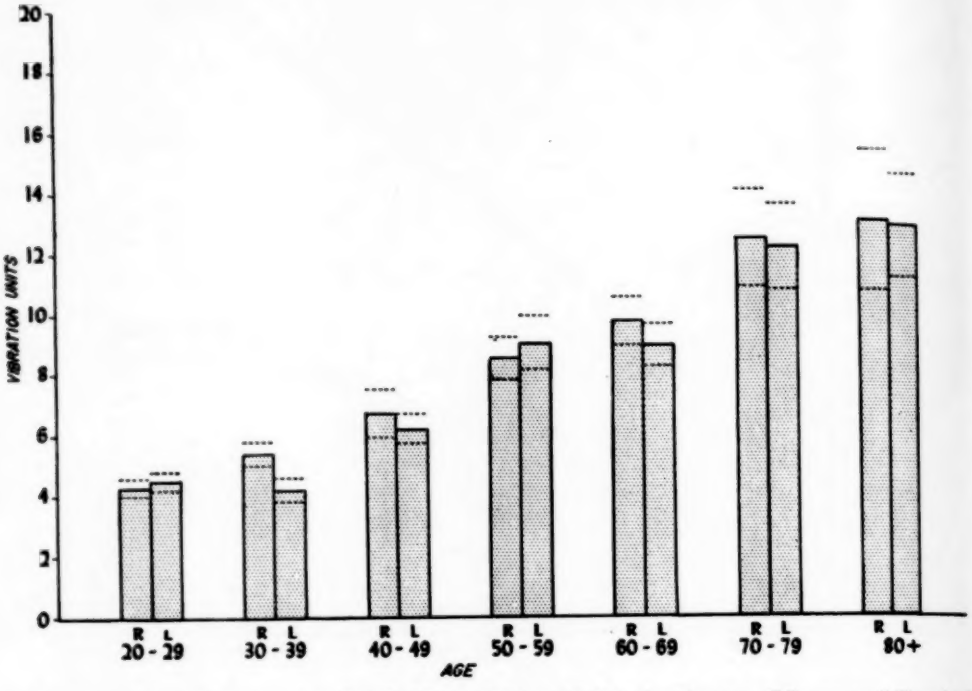

FIG. 6. *Vibratory perception thresholds of right and left index fingers.* (Means and Standard Errors).

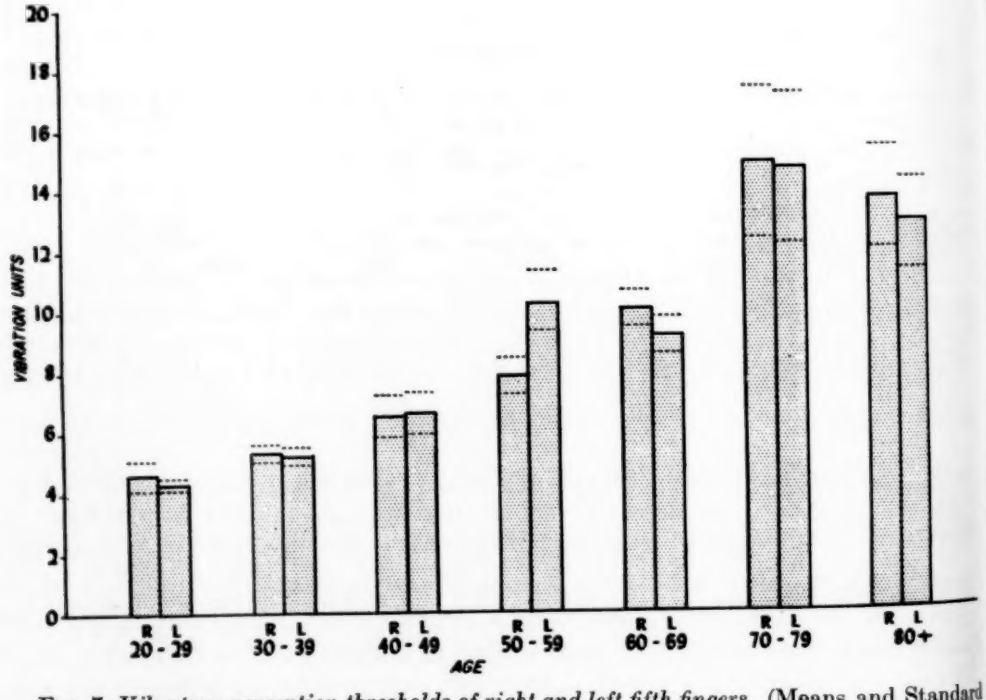

FIG. 7. *Vibratory perception thresholds of right and left fifth fingers.* (Means and Standard Errors).

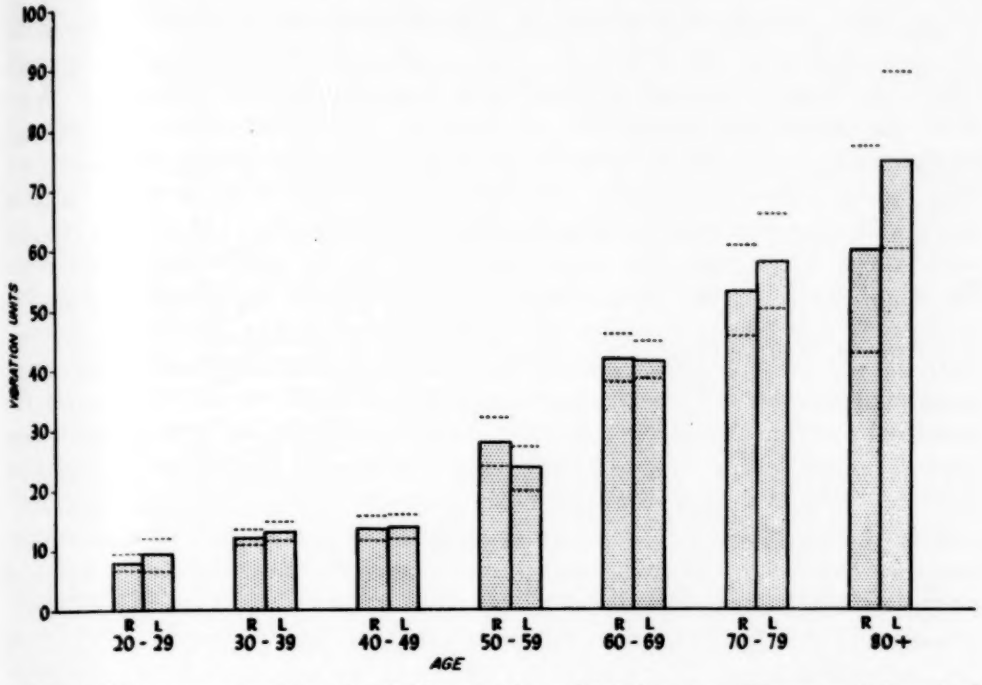

FIG. 8. *Vibratory perception thresholds of right and left big toes.* (Means and Standard Errors).

TABLE 2

Vibratory Perception Thresholds. Significance of Statistical Comparison Between Fingers and Toes

Index Finger and Corresponding Toe		Age of Subject (yrs.)	Fifth Finger and Corresponding Toe	
Right	Left		Right	Left
$0.05 > P > 0.02$	$0.2 > P > 0.1$	20–29	$0.05 > P > 0.02$	$0.20 > P > 0.1$
$P < 0.001$	$P < 0.001$	30–39	$P < 0.001$	$P < 0.001$
$0.01 > P > 0.001$	$0.01 > P > 0.001$	40–49	$0.01 > P > 0.001$	$0.01 > P > 0.001$
$P < 0.001$	$P < 0.001$	50–59	$P < 0.001$	$0.01 > P > 0.001$
$P < 0.001$	$P < 0.001$	60–69	$P < 0.001$	$P < 0.001$
$P < 0.001$	$P < 0.001$	70–79	$P < 0.001$	$P < 0.001$
$0.01 > P > 0.001$	$0.01 > P > 0.001$	80+	$0.05 > P > 0.02$	$0.01 > P > 0.001$

DISCUSSION

It has been suggested that the impairment of vibratory perception with increasing age is due to ischemic changes in the spinal cord (2), but most investigators ascribe the impairment to ischemic changes in the peripheral nerves (9–14). Since arteriosclerotic changes are common in old age and are more marked in the lower extremities (15), this would explain the greater impairment of vibratory perception in the feet. However, as confirmed in the present study, there is a significant difference in the perception threshold between the fingers and toes, even in young subjects. One might speculate that the difference in

young subjects is due, not to ischemic changes, but rather to a basic difference in the sensory innervation of these two parts of the body. In the present study every effort was made to use only subjects with normal peripheral circulation; therefore, the progressive impairment of vibratory perception with increasing age cannot be explained on the basis of any gross circulatory deficit. However, it is well known that arteriosclerotic changes in the vessels of the lower extremities are a more or less normal accompaniment of advancing age (16). These changes may not be evident clinically, as they may occur in the finer vasculature and not be demonstrable by the usual methods of examination. For instance, using P_{32}, it has been shown that in old age the capillary circulation is altered in association with altered efferent diffusion rates, even in the absence of clinically significant arteriosclerosis (17). These changes might be sufficient to affect adversely the nutrition and function of the sensory end-organs and nerves. It is possible, also, that alterations occur in these structures independent of circulatory and diffusion defects, along with other well known changes in the skin and its appendages (18).

Clarification of this problem is of interest in relation to the increased impairment of peripheral vibratory perception in patients with diabetes mellitus—a change which has been demonstrated quantitatively (9, 19). The etiology of this impairment is still uncertain; it has been suggested that it may be related to as yet unclarified metabolic disturbances (20) or to the accelerated development of arteriosclerosis in such patients (9, 11, 13). Since the present study indicates that impairment of peripheral vibratory perception may occur in normal subjects independently of clinically significant arteriosclerosis, it is possible that the increased impairment observed in diabetes may likewise be independent of the accelerating effect of this disease on peripheral arteriosclerosis, although the latter undoubtedly would be an added factor. As Loeb (21) has suggested, it is probable that multiple factors play a part in the development of the impairment of peripheral vibratory perception in diabetes. Studies of the peripheral circulation with Na^{24}—using the intravenous method of Friedell *et al.* and of Smith and Quimby (17, 22) and the clearance method of Kety (23)—in patients with diabetes mellitus with and without peripheral arteriosclerosis and in normal subjects, and correlation of such data with measurements of vibratory perception, would help to clarify this problem.

SUMMARY

Vibratory perception thresholds were measured in the fingers and toes of 100 normal male subjects who were from 22 to 85 years of age.

The vibratory perception threshold was higher in the toes than in the fingers at all ages and this was statistically significant in all but 1 instance.

There was a progressive increase in vibratory perception threshold with age at all the sites tested. This increase appeared to be logarithmic in nature.

The increase in vibratory perception threshold with age appears to be independent of gross circulatory deficits, but may be related to changes in the finer vasculature of the peripheral nerves and other peripheral tissues.

Acknowledgment

The author wishes to thank Mr. Eric Smith who developed and built the vibrometer, and Dr. D. H. Starkey of the Queen Mary Veterans Hospital for his constructive criticism of this paper.

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APPENDIX

This equipment (Figs. 9 and 10) is designed to supply a calibrated voltage to an ASTATIC M-41-8 recording head, fitted with a 1-inch long blunt needle.

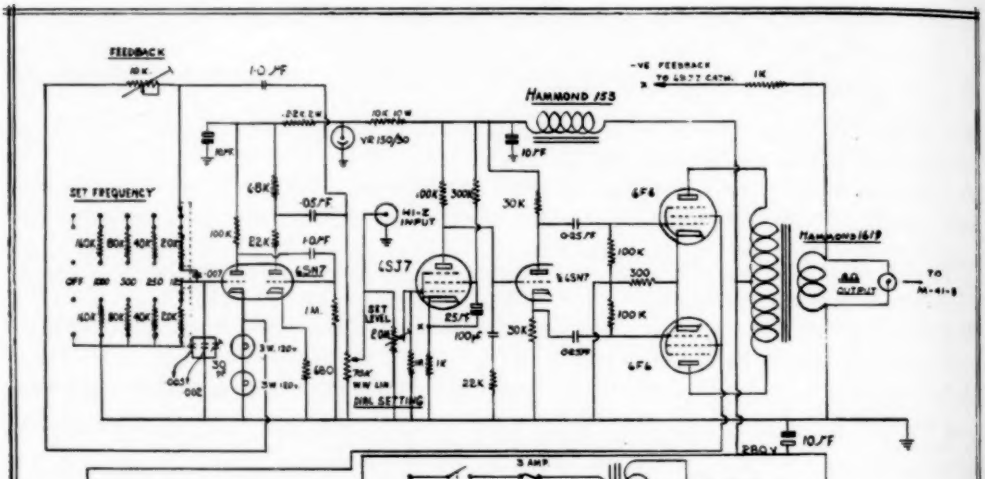

FIG. 9. *Circuit diagram of vibrometer.*

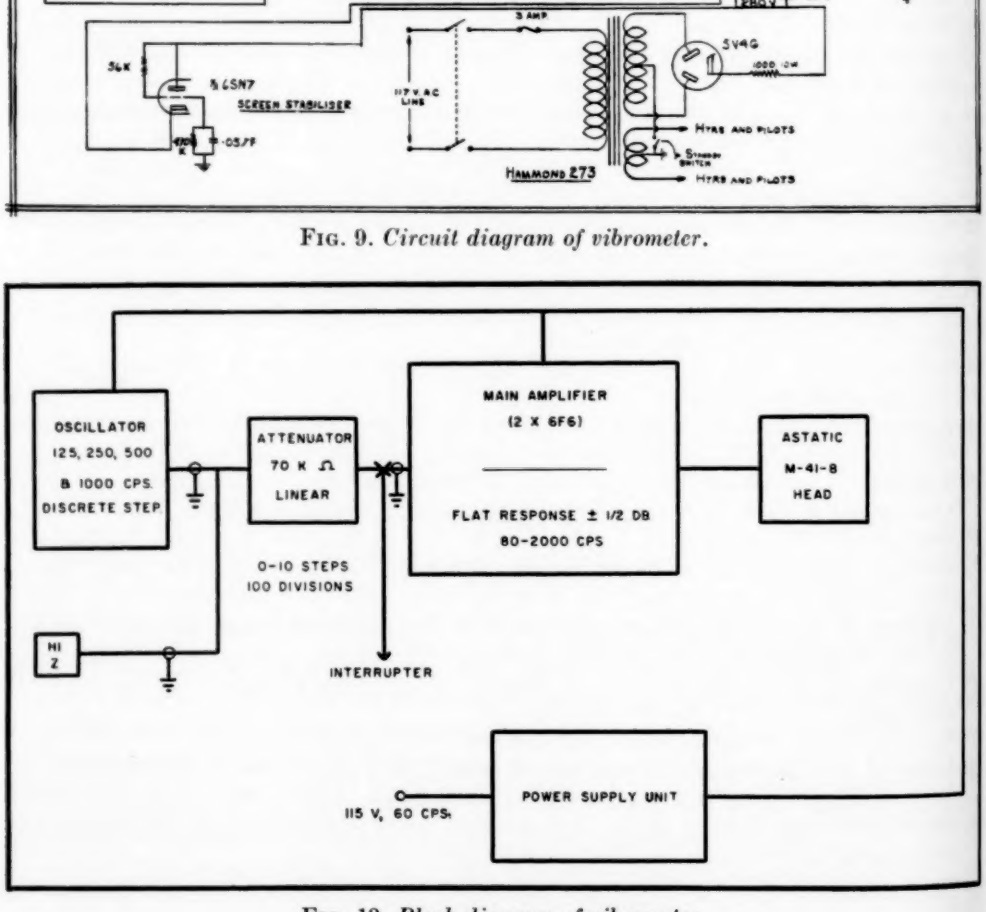

FIG. 10. *Block diagram of vibrometer.*

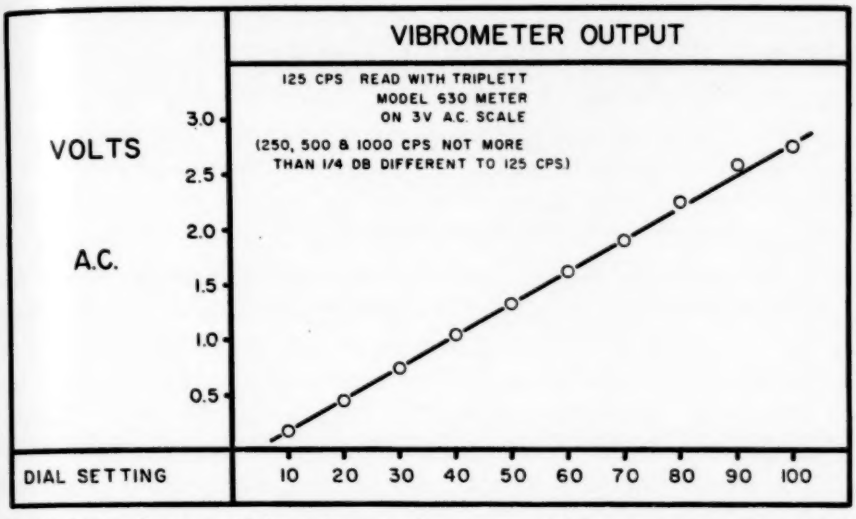

FIG. 11. *Relation between dial setting of vibrometer and vibrometer output in volts (A.C.).*

The oscillator section is an R. C. type, discrete frequencies of 125, 250, 500 and 1000 c.p.s. being available via a panel switch control. A pre-set feedback is provided. Plate voltage for the oscillator is stabilized by a VR 150/30 regulator tube and the output fed to a 70 K ohm wirewound linear potentiometer, calibrated in 100 equal divisions from 0–100. The controlled output is then coupled to the input of a push-pull 6F6 amplifier section which feeds an 8 ohm secondary winding to supply the recording head. Excellent stability is obtained by the use of negative voltage feedback and series electronic screen voltage control.

The power supply is conventional, and high impedance input and 8-ohm output are available for use of the amplifier alone (Fig. 11). An interrupter button grounds the input to the main amplifier for use during stimulation tests.

The whole is enclosed in a grey hammertone cabinet, the dimensions of which allow for efficient ventilation.

HOW PUBLIC HEALTH AND PRIVATE MEDICINE COOPERATE TO IMPROVE THE CARE OF THE OLDER PERSON*

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INTRODUCTION

State and local health departments are becoming increasingly aware of their responsibility to provide assistance to the private physician in meeting the many needs of the older patient. There is a growing recognition by public health officers and private physicians that the myriad problems engendered by an aging population are so complex and diversified that no single group, let alone a single individual, can provide all the services necessary for successful management of the patient. The private physician must be able to call upon a variety of professional skills and supporting resources that only can be provided through pooling of resources and cooperation among physicians, official and voluntary organizations, and industrial establishments.

That this cooperation has been successful in the past is manifested by the comparative freedom from the threat of acute communicable disease enjoyed in this country today. This great achievement in public health could not have been accomplished if each group within the community had acted independently. Already, official and voluntary agencies, utilizing techniques which have proved effective in controlling communicable disease, are establishing programs to deal with the problems of the chronically ill and the aged. As yet, however, there are no really comprehensive, community-wide programs in operation aimed specifically at solving the problems of chronic disease. Certainly the need for the provision of organized community services to reinforce the efforts of the private practitioner is far greater in the care of the chronically ill and aged than it was in the care of the patients with acute communicable diseases. So if this historical cooperation was able to produce such significant results in control of the communicable diseases, the results of similar cooperation should be no less successful in the area of chronic illness.

CHRONIC ILLNESS—A PUBLIC HEALTH PROBLEM

It is becoming more apparent that the health problems of older persons will continue to increase in volume and intensity as the numbers of this population group increase. Chronic disease with its residuals of disability has become the major public health problem in the United States. In 1950, an estimated 5.3 million persons were disabled three months or longer by chronic diseases, and

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almost 40 per cent (approximately 2.1 million) were 65 years of age or older. Of persons in the age groups under 45 years, 1.3 per cent were disabled by long-term illness; in the age group 45 to 64, the long-term disability rate was 5.8 per cent; and in the age group 65 and older it was 17.1 per cent (1). Coupled with the evidence that persons over 65 years of age require disproportionately more medical care than those in the younger age groups is the fact that old people are the least insured against the cost of long-term illness (2). Thus, we are confronted with an increasing tide of chronic disease and disability which may well have a profound effect upon our national life—medically, socially and economically.

Public health officers, as well as other health workers, whose activities during the past fifty years have been concerned with the communicable diseases are now being asked to provide many different types of services (direct and indirect) involving chronically ill and older persons (3). In light of these new demands, Winslow's definition of public health (4) is being re-examined by health officers in their desire to determine the extent of their responsibilities in the field of chronic illness and health of the aged. ". . . Public health is the science and art of preventing disease, prolonging life, and promoting physical and mental health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in the principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health."

Certainly, chronic illness which requires "organized community effort" for its control can readily qualify as a public health problem. There is extensive disability resulting from chronic diseases. Victims of chronic disease require medical and nursing care, nutritional aid, physical therapy, and home care services which involve a variety of professional groups and special facilities. Many persons suffering from a chronic disease have meager resources to tide them over a period of long-term illness and need assistance from official and voluntary agencies. There already has been an enormous drain on the public purse to pay for the health care bills of indigents, many of whom have become indigent because of a chronic illness. There is a need for community-wide programs for early detection of chronic illness in an attempt to prevent disabilities.

Although persons of all ages can be afflicted with chronic disease, proportionately more older persons are thus stricken. If the health problems related to aging are tackled vigorously and considered within the realm of public health, requiring cooperation on all fronts, positive results can be forthcoming. Considering "aging" as a chronic, progressive disease, it lends itself to epidemiologic and analytical study and to programs that will ameliorate its effects on the individual. This appears to be a more realistic and, in the long run, a more encouraging way to view this subject. However, as long as old age is considered in a euphemistic manner as the period of the "golden years," older people will feel a definite uneasiness. To many of these persons this period is anything but golden. Obviously, the later years can be a much healthier and happier period for many more per-

sons, but it is difficult to believe that the time of life when illness and disability rates soar is a golden period. Even the fortunate few who are able to maintain their functional capacity at a relatively high level suffer from the progressive diminution of physical, mental and social reserves which characterizes aging (5), albeit not to such a severe degree as the average older person.

COMMUNITY PROGRAMS

If, then, it is granted that older people have greater health problems and that these are, at least in part, public health problems, what is being done to encourage "organized community effort" and to develop resources to assist the private physician in the management of his patient? We find programs emerging in various areas of the country which emphasize the following: 1) early diagnosis and referral of patients to private physicians by health education methods and by specific disease case-finding techniques; 2) provision of "common denominator" services for the care of chronically ill patients (restorative services, organized home care, nursing home care); and 3) promotion of optimum health among people in the older age groups by the development of health-related services.

Early diagnosis

The development of techniques for the detection of disease in its early stages is a prerequisite to an effective attack on chronic disease. The private physician is hampered by not being able to detect disease until the patient presents himself for examination. Health education media are employed to help the public understand the importance of early diagnosis before the appearance of clinical disease and to motivate people to seek periodic health examinations. Such campaigns assist private practitioners by assuring earlier opportunities to detect disease—before disabilities have resulted. Community-sponsored case-finding projects for specific diseases involve the referral of individuals who are suspected of having the disease to private physicians for diagnosis and for appropriate treatment. This cooperative relationship is familiar in the case of tuberculosis and is becoming more so in regard to cancer, diabetes and glaucoma programs.

In Nashoba, Massachusetts, a "well oldster conference" is sponsored jointly by the Worcester District Medical Society and by the local health department. This project, based on the tested principle of the well-baby clinic, provides complete examinations without cost to apparently well persons aged 65 and older. Those who are found to require additional diagnostic services and treatment are referred to their private physicians.

The Santa Cruz County Health Department in California has organized a clinic which provides a complete physical and laboratory examination for all recipients of old age assistance (6). Patients who require medical services are referred to private physicians on a fee-for-service arrangement. Although it is too early to state definitely, it appears that this arrangement may lead to reduction in the costs of maintenance care, such as in nursing homes.

Mass case-finding programs often utilize screening tests to disclose incipient disease in persons who are apparently well. A single test (*e.g.*, blood sugar test for

diabetes, tonometric test for glaucoma) or a series of tests (multiple screening) are employed in a number of communities in such screening programs sponsored by State and local health departments (7). Projects such as these clearly complement and reinforce, rather than compete with the efforts of practicing physicians in a community.

Common denominator services

Medical management of patients with chronic disease often requires varying combinations of other supporting or "common denominator" services. These generally include organized home care services, restorative services for those who do not have a vocational goal, nursing home care, visiting nurse care, homemaker service, and dietary service. Any one or a combination of these may influence considerably the prospect of attaining the therapeutic goals which the physician has set for his patient.

Organized home care. In those communities where organized home care programs exist, a patient who no longer requires the intensity of the medical and nursing care services available in the hospital may be discharged to his home where, through coordinated efforts directed by a physician, comprehensive care services are provided. These may include nursing services, social services, physical therapy, occupational therapy, speech therapy, homemaker services, health education, medications, medical supplies, and orthopedic appliances. A study of organized home care programs completed by the Council of Medical Service of the American Medical Association (8) reveals a variety of sponsoring arrangements. Data on 31 organizations which reported a home care program in operation reveal that 22 are operated by private, nonprofit, community-supported agencies; and 9 are administered by public agencies or institutions such as health departments, welfare departments, or county hospitals.

The Commission on Chronic Illness suggests (9) that "most long-term patients can best be cared for at home during much of their illness and prefer care in that setting under supervision of their personal physician." It concludes that "home care programs organized to provide auxiliary services to the private physician offer the most effective method yet devised for bringing to long-term patients at home and to their families the coordinated services required." Obviously much remains to be accomplished in the development of such programs.

Homemaker service. Many older people are able to stay out of institutions and to maintain independent living as a result of assistance with housekeeping tasks by trained people. Assistance may range from once-a-week heavy cleaning service to a full-time, resident homemaker for extended periods. Such services can lead to a saving in tax funds, since it costs far less than medical care in most institutions.

Nursing homes. Nursing homes offer an environment for care of the patient which is intermediate between that of the hospital and the patient's home. A considerable number are operated under private ownership. We find that about 90 per cent of the patients in these homes are 65 years of age and older, the average age being 80 years. Of those in nonproprietary homes only about 80 per cent are in the older age groups (10). Nursing homes vary considerably in the quality

of facilities and care they provide. Health departments in 43 states have the responsibility for licensure of these homes, and consultative services by these agencies will do much to upgrade the level of the care they provide.

Restorative services. The problem of overcrowding of hospitals and nursing homes by the chronically ill and disabled patient can be attacked by provision of rehabilitative services to help restore the patient to the highest possible degree of self-care. The New York State Department of Health is sponsoring a statewide survey to determine the need for restorative services for patients in public nursing homes. Those patients who are found to have some potential for restoration to self-care are transferred to the rehabilitation hospital which the State health department operates at West Haverstraw, New York. Plans are being made to develop regional rehabilitation hospitals to provide restorative services in more conveniently located facilities throughout the State.

Promotion of optimal health (health-related services)

Health departments traditionally have regarded the promotion of optimum health as a major objective of their programs. Health education programs developed and sponsored by health departments have aided measurably in motivating the public to develop desirable health habits, to understand and seek immunization against communicable disease, and to participate in tuberculosis, diabetes and cancer case-finding projects. The impact of the health problems of older people is just beginning to be felt. Health departments are being called upon increasingly to provide or to stimulate the community to provide facilities and services to deal with the health problems of the aged (3). Health departments can serve as catalysts in organizing and involving the participation of individuals and community groups in the continuing campaign against disease and disability.

Housing. Obviously, home care programs cannot function satisfactorily in a poor environment, and it is known (11) that older people are not, in general, well housed. In many instances the homes may be too large, or otherwise unsuited to the needs of the older person; many persons, because of inadequate funds, are forced to live in substandard rooms or apartments in cheap-rent districts. The stimulation of enactment and the enforcement of an occupied-dwelling ordinance will do much to upgrade substandard housing. This cannot fail to have a beneficial effect upon the health of older people.

Recreation. The experience of Hodson Center (12), showing that older people who participated in a group recreation center for six months required 38 per cent fewer medical clinic visits than they did prior to this participation, clearly points to the interrelationship between organized recreation and physical health.

Counseling. Case-work counseling assists the older person to adjust to realities and at the same time gives him an opportunity to discuss his emotional problems with a sympathetic listener. Closely related with this service is the "central referral service for the chronically ill," which permits a specialized agency to concentrate on finding the appropriate community resource for a particular patient.

Adult education programs lead to an enrichment of life and add meaningfulness to the extended existence medical science has provided. Such programs should be

held in the daytime, since many older people do not like to go out at night, and should be geared to the lower educational level of the people in the older age groups.

Community organization

In all of these activities, it is not implied that only the health department can start and administer such services. Many programs are being carried out in private agencies, welfare departments and departments of education; nevertheless, health departments can, and in many instances actually do, operate these services. At a minimum, however, the health officer should concern himself with the need to initiate such programs, so that they are available when needed. The community will decide whose auspices are best for a particular program; but when the health officer takes the initiative in its early development, the community may well decide he should have responsibility for all of it.

Clearly, medical societies should participate in all planning at the earliest stages. Problems presented to them as such will receive objective study; medical societies are more likely to look askance on cut-and-dried programs which are brought in for their blessing. Coordination of activities is not possible unless the programs result from the mature consideration of a community problem by people who have the courage of their convictions and the willingness to examine all facets with open minds. This applies to health officers as well as to medical societies and other community groups.

SUMMARY

It is the responsibility of the health officer to appeal to the conscience of the community to plan for and develop health programs for the older segment of the population which support and complement the services which private physicians are trained to provide. The health officer, in turn, can expect that the private physician will offer his patients a high quality of medical care based on the tradition of physician-patient relationship. As the potential of this mutually supporting partnership in health becomes more widely understood, the benefits to man will increase correspondingly.

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OCCULT MYOCARDIAL INSUFFICIENCY

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Intermediate coronary syndrome (1), severe angina (2–4), prodromal symptoms of myocardial infarction (5, 6), and impending acute coronary artery occlusion (7) are familiar terms well defined in medical literature. The clinical stage preceding these conditions, however, is not sufficiently well understood. The problem is how to recognize and treat occult myocardial insufficiency while the indicative signs are lacking. Without such recognition and treatment, an occasional patient, after complete examination including electrocardiography and a roentgenogram of the chest, will be found in good physical condition but within a short time will experience acute decompensation or acute coronary occlusion (8). This report concerns our clinical observations and experience with the use of a diuresis test as an aid in verifying the diagnosis of occult myocardial insufficiency.

CLINICAL AND LABORATORY OBSERVATIONS

Forty-eight patients were treated for occult myocardial insufficiency with diuretics (Table 1). Of the 48 patients, 47 were followed for periods of from one to nine years (Table 2). Of the group, 20 were men aged 32 to 76 years and 28 were women aged 33 to 73 years (Table 3). Twenty-six women were amenorrheic due to physiologic or surgical causes. All 48 patients had some impairment of circulation, as indicated by an increased circulation time which improved with treatment.

In a typical instance the patient had felt that something was amiss and had visited his physician, usually after futile self-medication. He did not want assurance that all was well but had sought relief from his symptoms. These included 1) persistent fatigue despite normal rest, 2) inability to take a deep breath and episodes of yawning or sighing, or both, and 3) nocturia one or more times nightly, usually within three hours after retiring and with the passage of a greater quantity of urine than during the daytime.

Physical examination and laboratory findings, although showing no definite abnormalities, revealed 1) fine or coarse rales at the bases of both lungs, 2) a slight alteration in the blood pressure from prior readings (plus or minus 10 mm. Hg), 3) an increase in the circulation time (arm to tongue) following injection of calcium gluconate, from a normal rate of 10 to 15 seconds to more than 20 seconds, 4) a pulse rate above 100, 5) no peripheral edema, 6) a normal electrocardiogram, 7) a normal chest roentgenogram, and 8) an erythrocyte sedimentation rate within 10 per cent of normal.

The therapeutic test used to verify the diagnosis of occult myocardial insufficiency consists of the intramuscular injection of 0.5 cc. of a mercurial diuretic

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TABLE 1

Response of 48 Patients with Occult Myocardial Insufficiency to Treatment with Diuretics

Patient No.	Age and Sex	Occupation	Initial Complaints*	Date Treatment Begun	Cardiac Status at Outset†	Circulation Time (sec.) Arm to Tongue		Response to Diuretic‡	Cardiovascular Complications	Resulting Cardiac Status†
						First	Last			
1	62 M	Laborer	1-2-3	Aug. 1952	II	25	16	xxx	None	I
2	66 M	Jeweler	1-2-3	Apr. 1956	II	22	15	xx	None	I
3	61 F	Housewife	1-2-3	Oct. 1955	II	23	12	xx	None	I
4	59 F	Maid	1-2-3	Oct. 1949	III	28	20	xx	None	II
5	52 M	Laborer	1-2-3	July 1955	II	25	17	xx	None	I
6	73 F	Housewife	1-2-3	July 1955	III	23	12	xxx	None	I
7	61 F	Maid	1-3	Jan. 1955	III	28	12	xxx	None	I
8	43 M	Accountant	1-2	Jan. 1957	II	23	14	xx	None	I
9	72 F	Housewife	1-2-3	Oct. 1952	II	24	20	xx	None	II
10	55 F	Housewife	1-2-3	Aug. 1955	III	28	18	xx	None	II
11	46 F	Professional	1-2-3	Dec. 1948	II	26	14	xx	None	I
12	76 M	Clergyman	2-3	Apr. 1955	II	20	14	xx	None	I
13	40 F	Housewife	1-2-3	May 1952	II	23	5	xxx	None	I
14	47 M	Machinist	1-2-3	May 1956	II	21	8	xx	None	I
15	48 F§	Professional	1-2-3	June 1948	II	21	8	xx	None	I
16	54 F	Housewife	1-2-3	Dec. 1953	III	25	16	xx	Angina	II
17	47 M	Cook	1-2-3	Feb. 1948	II	23	17	xxx	Peripheral vascular	I
18	49 F	Clerk	1-2-3	May 1954	II	25	18	xx	None	I
19	54 F	Nurse	1-2-3	Apr. 1956	II	23	14	xx	None	I
20	43 F	Housewife	1-2-3	July 1951	II	23	10	xx	None	I
21	66 F	Housewife	1-2-3	Oct. 1949	III	35	15	xxx	None	I
22	55 M	Construction worker	1-2-3	Oct. 1953	III	27	—	xx	Coronary occlusion	Died
23	57 F	Housewife	1-2-3	Feb. 1951	III	25	10	xx	None	I
24	61 F	Housewife	1-2-3-4	Nov. 1953	II	23	12	xx	Rectal bleeding	I
25	58 M	Salesman	1-2-3-5	Aug. 1956	III	23	15	xxx	None	I
26	42 F§	Accountant	2-3-4	June 1956	II	22	12	xxx	None	I
27	55 F	Telephone operator	1-2-3-4	Apr. 1953	III	27	12	xxx	None	I
28	56 M	Laborer	1-2	Jan. 1956	II	22	15	xx	None	I
29	50 M	Builder	1-2-3	Dec. 1955	III	27	17	xx	None	I
30	58 F	Clerk	1-2-3	Oct. 1953	II	22	10	xx	None	I
31	38 F	Professional	1-2-3-5	Oct. 1954	III	25	15	xx	Peripheral vascular	I
32	54 M	Laborer	1-2	Sept. 1956	II	22	12	xx	None	I
33	50 F	Superintendent	1-2-3	Jan. 1950	II	25	15	xxx	None	I
34	49 F	Factory worker	1-2-3	Aug. 1956	III	27	10	xx	None	I
35	43 M	Laborer	1-2-3	Feb. 1956	II	25	19	xx	None	II
36	52 M	Salesman	1-2-3	May 1948	III	27	12	xxx	None	I
37	45 F	Housewife	1-3-5	Nov. 1955	III	25	20	xx	None	II
38	39 M	Laborer	1-5	Nov. 1956	III	26	19	xxx	None	I
39	46 F	Waitress	1-2	Sept. 1956	II	20	12	xx	None	I
40	32 M	Shop manager	1-2-3	Oct. 1955	II	23	13	xx	None	I
41	66 F	Housewife	1-2-3	Nov. 1952	II	24	20	xx	None	II
42	45 M	Superintendent	1-2-3	Nov. 1951	II	24	8	xx	Peripheral	I
43	54 F	Housewife	1-2-4	Jan. 1956	III	28	8	xxx	None	I
44	33 F	Maid	1-2-3	Oct. 1955	II	22	13	xx	Rectal bleeding	I
45	63 M	Barber	1-2-3	May 1956	II	22	13	xx	None	I
46	39 F	Housewife	1-2-3	May 1954	II	22	17	xx	None	I
47	59 M	Waiter	2-3-5	Sept. 1955	III	28	16	xx	Rectal bleeding	I
48	40 M	Clerk	1-2-3	Sept. 1950	III	28	17	xx	Rectal bleeding	I

* 1 = Persistent fatigue.
2 = Inability to take a deep breath.
3 = Nocturia.
4 = Edema of lower extremities.
5 = Rectal bleeding.

† I = Cardiac disorder without limitation of physical activity. Ordinary physical activity caused no discomfort; II = Cardiac disorder with slight to moderate limitation of physical activity. Ordinary physical activity caused discomfort; III = cardiac disorder with moderate to great limitation of physical activity. Less than ordinary physical activity caused discomfort.

‡ Each "x" indicates 500 cc. of urine passed during the hours following injection of a diuretic substance.

§ Menstruant.

TABLE 2

Years Under Observation

Less than	Males	Females	Total
1 yr.	6	4	10
2 yrs.	8	6	14
3 yrs.	0	4	4
4 yrs.	1	4	5
5 yrs.	1	3	4
6 yrs.	1	1	2
7 yrs.	1	1	2
8 yrs.	0	3	3
9 yrs.	2	2	4
Total	*20*	*28*	*48*

TABLE 3

Age at Onset of Symptoms

Age (yrs.)	Males	Females	
		Amenorrheic	Menstruant
32–39*	2	3	
40–49	6	7	2
50–59	8	9	
60–69	3	5	
70–76*	1	2	
Total	*20*	*26*	*2*

* Limits for females, ages 33 and 73.

such as Dicurin or Mercuhydrin. A positive response is manifested by the passing of 500 to 1000 cc. more than the normal amount of urine during the next six to twelve hours (4). The circulation time will then return to less than 20 seconds, and the primary symptoms will gradually disappear.

The plan for treatment consisted of the intramuscular injection of 0.5 cc. of Dicurin or Mercuhydrin weekly until no extra urine was passed and the circulation time returned to normal, restriction of smoking, reduction in sodium intake, and reduction of excess weight to within 5 pounds of that listed in a standard weight table. Periodic observations were made as a safeguard against recurrences.

CASE REPORTS

The following 3 case reports illustrate the reversal of occult myocardial insufficiency through the use of diuretics, and show what can be accomplished when the prodromal symptoms are recognized and appropriate action taken, instead of waiting for a cardiac catastrophe to occur.

Case 1

Wm. Mc., a man 45 years of age, was first seen on November 23, 1951, complaining of nocturia (three times nightly) for the previous four weeks, tiredness for the previous three weeks, and difficulty in taking a deep breath for the previous two weeks.

The blood pressure was 140/80 and the pulse rate 110. Rales were present in both lung bases. A roentgenogram of the chest showed no abnormalities. The circulation time (arm to tongue) was 24 seconds. The patient weighed 177 pounds and had gained 8 pounds in the preceding seven months.

At this and each subsequent visit, 0.5 cc. of Mercuhydrin was injected intramuscularly. The patient was instructed to take 7.5 grains of ammonium chloride three times daily.

On November 26, the patient felt better. Urine volume was 1200 cc. in six hours following injection of Mercuhydrin. He had nocturia once nightly and slight chest pain upon exertion. At this time, the blood pressure was 120/80 and pulse rate 96. An electrocardiogram showed no abnormalities. The erythrocyte sedimentation rate was 10 mm. in 43 minutes (Cutler). His weight was 174 pounds.

The patient returned on December 1 without complaints. Urine volume following injection of Mercuhydrin was 500 cc. in six hours, the blood pressure was 100/80, and pulse rate 72. A few rales were still present in the left lung base. The circulation time was 16 seconds.

On December 7, the patient had no complaints. Urine volume following injection of Mercuhydrin was 200 cc. in six hours, blood pressure 110/80, pulse rate 70, erythrocyte sedimentation rate 10 mm. in 47.5 minutes, circulation time 8 seconds, and body weight 171.5 pounds.

On December 18, the patient was free of complaints. Urine volume following injection of Mercuhydrin was 100 cc. in six hours, blood pressure 110/80, pulse rate 70, circulation time 8 seconds, and weight 168 pounds.

This man has been treated regularly five times per year since December, 1951. His weight has decreased to 151 pounds. The blood pressure is 120/80. He has remained asymptomatic but has continued to receive 0.5 cc. of Mercuhydrin intramuscularly at each visit.

Case 2

H.G., a 35-year-old woman who had undergone a hysterectomy, was apprehensive but not in acute distress when seen on February 25, 1956. She complained of fatigue, nocturia twice nightly, and intermittent sleep at night—all of two months' duration—and difficulty in breathing, of three weeks' duration.

At the initial examination, the blood pressure was 120/100, the pulse rate 104, and weight 155 pounds. Rales were present in both lung bases. The circulation time was 23 seconds. The electrocardiogram was within normal limits. A roentgenogram of the chest showed no abnormalities. The erythrocyte sedimentation rate was 10 mm. in 60 minutes (Cutler).

This patient was treated by the intramuscular injection of 0.5 cc. Dicurin *at this and each subsequent visit*. She was directed to take 7.5 grains of ammonium chloride three times daily.

By February 27, the patient's physical and mental condition had improved. Nocturia was reduced to once nightly. Urine volume was 2000 cc. during the six hours following the injection of Dicurin. The blood pressure was 160/110, pulse rate 96, and weight 153 pounds. Rales were still present in the bases of the lungs. The circulation time was 21 seconds. The dose of Dicurin was repeated.

On March 3, the patient felt less tired but complained of slight pain in the chest upon exertion. Nocturia was still once nightly. Urine volume was 1000 cc. during the six hours following the injection of Dicurin. The blood pressure was 130/80, pulse rate 84, and weight 151¾ pounds. Pulmonary rales had disappeared. The circulation time was 19 seconds.

The patient had no complaints when seen on March 10 and no nocturia. Urine volume was 500 cc. during the six hours following the injection of Dicurin. The blood pressure was 110/80, pulse rate 80, and weight 150½ pounds. The circulation time was 17 seconds.

On March 24 the patient had no complaints. Urine volume was 100 cc. during the six hours after the injection of Dicurin.

Case 3

M.S., a 66-year-old man, was first seen on April 17, 1956, complaining of tiredness of six months' duration, a chronic cough of three years' duration, nocturia two or three times nightly for a period of four or five years, difficulty in breathing of one month's duration, difficulty in taking a deep breath of four months' duration, pain in the right and left posterior thorax present for three months, and a feeling of tension present for four months.

The blood pressure was 120/80, pulse rate 108 with regular sinus rhythm, and weight 137 pounds. Coarse rales were present in both lung bases. A roentgenogram of the chest and an electrocardiogram showed no abnormalities. The circulation time was 22 seconds, and the erythrocyte sedimentation rate was 10 mm. in 60 minutes.

Treatment consisted of the intramuscular injection of 0.5 cc. of Dicurin *at this and each subsequent visit*, the ingestion of 7.5 grains of ammonium chloride three times daily, and a low-sodium diet.

On April 24, the patient felt well and had lost the feeling of tension. Nocturia was reduced to once nightly. Urine volume following injection of Dicurin was 1000 cc. in six hours. His breathing ability had improved. The blood pressure was 120/80, pulse rate 90, and weight 136 pounds. A few rales persisted in the lung bases. The circulation time was 17 seconds.

On May 3, the patient had no complaints. Nocturia was still once nightly. Urine volume following injection of Dicurin was 300 cc. in six hours. The blood pressure was 120/80, pulse rate 72 with a regular sinus rhythm, and weight 136½ pounds.

On May 17, the patient was still free of complaints. The blood pressure was 110/70, pulse rate 72, and weight 137¾ pounds. The lungs were clear. He passed 100 cc. of urine in six hours following injection of Dicurin.

In contrast to the preceding 3 cases, Case 4 illustrates that, even with the proper recognition of occult myocardial insufficiency, cardiac catastrophe cannot be prevented unless the patient is willing to cooperate with the plan of management.

Case 4

G.C., a male construction worker, 55 years of age, was first seen on October 8, 1953, complaining of difficulty in taking a deep breath of three weeks' duration, nocturia three times nightly of five weeks' duration, and a feeling of tiredness of four weeks' duration.

The patient had gained 24 pounds in nineteen months. Rales were present throughout the chest. The pulse rate was 115 with regular sinus rhythm, and the blood pressure was 190/100. The circulation time was 27 seconds. There was no peripheral edema.

The patient was given an intramuscular injection of 0.5 cc. of Mercuhydrin, and instructed to take 7.5 grains of ammonium chloride and 0.5 grain of phenobarbital three times daily. He was directed to rest, to remain away from his occupation for one week, and to adhere to a salt-free diet.

Contrary to advice, this man returned to work the following day (October 9, 1953) because he felt well again. During the afternoon, he complained of a burning sensation in his chest but finished the day's work and returned home.

At 6:00 A.M. on October 10, the patient's wife reported by telephone that he was complaining of severe pain in the chest. He had acute coronary occlusion and died at 6:15 A.M. of cardiac arrest.

SUMMARY

Forty-eight cases of occult myocardial insufficiency are presented, 47 of which have been followed for periods up to nine years. One fatality occurred in a

patient who failed to comply with the plan of management. This case and 3 cases successfully managed with diuretics are reported in detail.

Occult myocardial insufficiency is the earliest stage at which the physician can recognize impending cardiac catastrophe. The features peculiar to this syndrome are fatigue, inability to breathe deeply, and nocturia.

In the absence of significant physical or laboratory findings except increased circulation time, the diagnosis can be verified by the response to intramuscular injection of a mercurial diuretic. In occult myocardial insufficiency the response is characterized by a decrease in circulation time and the gradual disappearance of the primary symptoms.

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AFFECTIVE TONE IN HUMAN FIGURE DRAWINGS BY INSTITUTIONALIZED AGED AND BY NORMAL CHILDREN*

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In clinical usage the drawing of the human figure is frequently considered to convey aspects of self image. Clinical psychologists have held that detailed analysis of such drawings provides a basis for inferences about the drawer's intellectual level (1), his areas of emotional conflict (2), and his concept of self (3). Utilizing this graphic technique, the writer has attempted to study the reflected discrepancies in body image between 2 disparate groups—institutionalized aged and normal children.

The notion that aging effects changes in self image is consistent with Schilder's theory of the vissicitudes in body image (4). According to this theory, the image of the body is based upon an emotional mood which is, in turn, based upon biologic status. The changes in the biologic unit reflect themselves in the plastic image of the body. Thus, in theory, we would be led to anticipate that persons who undergo the physiologic processes and who experience the psychologic stresses associated with aging might reflect some corresponding changes in self-image as projected in their drawings of the human figure.

Investigation of human figure drawings by the aged has, in fact, revealed certain characteristics which distinguish them from drawings by younger normal subjects. Clinical reports and manuals (2, 3) have indicated that measurable differences may be seen in such factors as height or size of figure. The present writer systematically studied a constellation of formal characteristics of figure drawings by institutionalized aged and by normal children (5). The basis of the research was theory which has evolved from clinical practice in the analysis of drawings.

In clinical work, gross departures from "normative" performances in terms of such formal variables as area, height and centeredness of drawings are frequently interpreted as evidence of deviant intrapersonal states. Area utilized, for example, is considered to reflect self-assessment in relation to the environment. Height is similarly interpreted as an indication of feelings of relative self-significance. Centeredness is often considered to be affected by the subject's general security level and by his orientation toward reality. The relative freedom of these indices from previous artistic training and from conscious control made them excellent points of comparison between contrasting groups. The writer found that institutionalized aged drew smaller, shorter and less well centered figures than did the children.

* Data on the aged for this study were gathered at the Drexel Home for the Aged and at the Orthodox Jewish Home for the Aged, Chicago, Illinois. Thanks are due the staffs of these institutions for their cooperation.

Qualitative factors have, to some extent, been investigated (6). However, the emphasis to date has been upon isolated factors which, in addition, may be rather sensitive to the unevaluated influences of previous training and experience. Such factors as proportionality, presence or absence of body parts, and presence or absence of clothing may be diagnostically significant. However, taken singly, they may be less important to an understanding of the drawer's self image than a more holistic impression. The point may be illustrated by a review of the manner in which an experienced clinician may proceed. He will certainly take account of the formal and qualitative features just mentioned. Then, more likely than not, he will rapidly integrate these as he attempts to "gain a feel" for the drawing. Thus, in order to try to understand the personality of the drawer, he endeavors to grasp the essential affective tone conveyed in the drawing. To use Schilder's terms, he attempts to achieve understanding of "the emotional mood" of the body or self image. It is toward investigation of this emotional mood or affective tone in the drawings of institutionalized aged as compared with that conveyed in the drawings by normal children than the present study was aimed.

PROCEDURES

Samples of human figure drawings by institutionalized aged and by normal children were shown to clinical psychologists who were asked to make descriptive comments about them. From the list of descriptive comments given, a series of adjective pairs was constructed. The 10 adjective pairs utilized reflected the following polar concepts: full-blooded *vs.* anemic; life *vs.* death; virility *vs.* impotence; growth *vs.* decay; striving *vs.* drifting; strength *vs.* weakness; happiness *vs.* misery; fullness *vs.* emptiness; moving *vs.* inert; and fleshy *vs.* bony. An 8-point scale for each of these dimensions was constructed for the purpose of rating the drawings.

Figure drawings by 10 randomly selected institutionalized aged of average intelligence and "good contact" and by 10 similarly selected normal and average third-grade children were utilized. The identifying data for the subjects whose drawings were judged are listed in Table 1. Since in the present study the aim was to see whether relative novices could gain holistic impressions from the drawings, it was decided to utilize non-psychologists as judges. Nine psychiatrists and psychiatric social workers who were relatively naïve with respect to analysis of figure drawing served as judges. They were completely unaware of the nature of either group of subjects being tested (this was confirmed in later interviews

TABLE 1

Identifying Data

Subjects	Mean Age (yrs.)	Education (yrs. of formal schooling)	No. of Males	No. of Females
Institutionalized aged (10 subjects)..	79.1	3*	6	4
Normal children (10 subjects).....	8.9	3	4	6

* Estimated, because of discrepancies in education of aged, who were all foreign born.

TABLE 2

Analysis of Variance of the Ratings of Figure Drawings by Institutionalized Aged and by Normal Children

	Sum S9	df	Mean Sg	F
Total	45407	1799		
Total between groups	4708	179	26.3	1.05
Age	3107	1	3107	123.8†
Adjectives	248	9	27.6	1.1
Judges	569	8	71.1	2.8*
Age × Adj	98	9	10.9	...
Age × Jud	133	8	16.7	
Adj × Jud	303	72	4.2	
Age × Adj × Jud	250	72	3.5	
Within	40699	1620	25.12	

* Significant at the .01 level.
† Significant at the .001 level.

with the judges. Most of them had guessed that *all* of the drawings were the work of psychotic adults.) The judges were instructed as follows: "A drawing of a person will be projected on the screen in front of you. It will be visible for just one minute, during which time you are asked to register your subjective reaction to it in terms of the dimensions you see on the rating sheets. Report your impression; don't think long; try to do it more or less on impulse."

Statistical treatment of comparisons between groups of subjects, judges' ratings, and affectively toned adjective pairs was by means of analysis of variance.

RESULTS

Table 2 shows the results of the analysis of variance of the data.

Differences between the drawings by the institutionalized aged and those by the normal children on each of the affectively toned adjective dimensions were significant (.001). According to the judges' ratings, the drawings by the aged more frequently conveyed the negative affects implied by the terms anemic, dead, impotent, decayed, drifting, weak, miserable, empty, inert and bony. Notwithstanding a tendency among several of the judges to rate all drawings uniformly high or uniformly low, there was general agreement among the judges with respect to direction of ratings and the differentiation between groups. The results reflected the performances of 2 internally homogeneous populations and were not the effect of extreme performances in either group.

DISCUSSION

Gross differences in self conceptualization and, presumably, in body and self image would be anticipated in a comparative study of these groups. Their life situations were somewhat similar in only one way: both groups were explicitly dependent upon protecting and nurturant environmental forces for gratification of primary needs. However, as contrasted with the vigor, growth, increasing

FIG. 1. Affective tones of human figure drawings by children (upper 3 figures) and by institutionalized aged (lower 3 figures).

self-awareness and recognition of potential among the children, the psychologic decrements and impairments accompanying physiologic changes in the aged are a matter of concern. Loss of self esteem, lessened vitality, and the sense of impending further decline are characteristic of institutionalized aged.

What is of primary significance is that the human figure drawings by the aged subjects do convey the sense of how they feel about themselves. The feelings of self-devaluation, apathy and hopelessness find graphic expression in their drawings (Fig. 1).

The fact that the affective tones of the drawings by the groups were differentiated by the ratings of relative novices in figure drawing analysis is significant. This lends support to the notion that the affective tones of the drawings were sufficiently potent to arouse a response. The general agreement among the

judges indicates a basically stable and reliable phenomenon. (Previous studies (1, 7) have already reported respectable reliabilities for formal aspects of figure drawing among the aged.) Homogeneity among the drawings of the groups suggests that the affective tone under study would characterize the drawings of any group of institutionalized aged.

Why do the adjective pairs uniformly differentiate the groups? It would seem that this reflects a fairly generalized affective status among the institutionalized aged. In a manner somewhat similar to the effects of a depressive reaction, many separate aspects of reaction potential are submerged beneath a totalistic gloom.

The question may be raised as to the primacy of organic impairment as a determining element in the affective quality of the figure drawings by these aged persons. To this argument there can only be the reply that the influences of these and personality factors in the execution of drawings cannot really be separated, but comprise a psychophysiologic matrix for the response to the instruction "draw a picture of a person." (In a previous paper, the writer noted the lack of relationship between constriction in drawings by the aged and their non-constricted Bender-Gestalt patterns.) In the terms of Schilder, one investigates in self-image an emotional mood based upon biologic tendencies.

Since the human figure drawing technique is sensitive to psychophysiologic status of the aged in terms of self-image, it might be further utilized in longitudinal investigations of modifications in self-image. Another question which might be studied would be the comparison between self-image, as reflected in the drawings of institutionalized and non-institutionalized aged. Here we might be able to differentiate between the psychophysiologic influences of aging per se, and those presumably related to such factors as relative independence of functioning and the effects of permanent custodial-protective care. A third area is the question of alteration in body or self-image as effected by environmental change, therapeutic program and the like. The technique would seem to provide a valuable tool in research and assessment with respect to the social-psychologic problems of the aged as well as in individual diagnostic evaluation.

SUMMARY

This study sought to investigate relationships between affective tone of figure drawings and self-image in the aged. Earlier research in a comparison of institutionalized aged and normal children revealed relationships between formal indices in drawings such as area, height and centeredness and psychophysiologic status. The present study emphasized the affective tone of the drawings. Randomly selected figure drawings of the 2 disparate groups (aged and children) were shown to 9 psychiatrists and psychiatric social workers who acted as judges. They were unaware of the nature of either group of subjects. Judges were asked to rate the drawings on an 8-point affective tone scale for 10 polar adjective pairs. Results revealed significant differences. The drawings by the aged consistently were more negative in tone for each of the dimensions. Direction of difference in tone rated was consistent with this notion of impaired self-image among the aged.

Psychophysiologic status as it affects self-image is reflected in human figure drawing by the aged. The technique holds promise for assessment of differences in self-image among various categories of aged, for study of longitudinal modifications in self-image, and for evaluation of programs of rehabilitation.

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THE MANAGEMENT OF MULTIPLE MYELOMA.

Adams, W. S., and Skoog, W. A. *J. Chron Dis.* **6:** 446 (Oct.) 1957.

The therapy of multiple myeloma at best is palliative. The bone pain that these patients almost universally suffer can be relieved by narcotics. However, it is desirable to discontinue them as soon as possible because of side-effects. This can be facilitated by adequate dosage with corticosteroids. Radiation therapy is effective in back pain not due to compression fracture of a vertebra associated with nerve-root compression. Only temporary relief of bone pain can be obtained with urethane, radioactive phosphorus, and stilbamidine. Only an occasional patient will escape a compression fracture of one or more vertebral bodies. Fractures of other bones may also occur. Therefore, periodic radiographic surveys of the skeleton to assess the involvement of weight-bearing bones is advisable in order to institute proper orthopedic care. Patients need to be cautioned against heavy lifting and activities that threaten the integrity of the skeleton. Orthopedic surgical procedures have proved universally unsuccessful. Neither increased calcium intake, vitamin D, nor testosterone will correct the demineralization of bone found in multiple myeloma. Hypercalcemia (serum values above 12 mg. per 100 ml.) occurs in 50 to 60 per cent of patients with multiple myeloma. The hypercalcemia syndrome occurs less frequently and is characterized by anorexia, nausea, vomiting, apathy, weakness, polydipsia, polyuria, intractable constipation, and drowsiness. Early recognition is essential in order to avoid serious consequences from the hypercalcemia. Treatment may include one or more of the following: high fluid intake, low calcium diet, corticoids and ACTH, sodium citrate to reduce the amount of ionized calcium in the blood, and chelating agents. Sodium ethylene diamine tetra-acetic acid, which chelates calcium, has as yet not been used sufficiently that it can be recommended for routine use. The most successful combination is probably hydration, with steroid therapy. Patients with multiple myeloma show decreased resistance to infection and the spread of infection is likely to be rapid. Therefore, the institution of antibiotic therapy before bacteriologic culture studies are completed may prove life saving. Blood transfusions offer only transient benefit in the normochromic, normocytic anemia almost invariably found in multiple myeloma. Transfusions should probably be reserved, because of the hazards that attend their use, for patients with severe anemia and those actively bleeding. Steroid therapy with prednisone may increase the hematocrit and hemoglobin values, but treatment with iron, liver or vitamin B_{12} has not proved successful in combating the anemia. The hemorrhagic manifestations of multiple myeloma are difficult to treat. Astringents, pressure packs, topical thrombin, and cauterization may prove effective in epistaxis. If thrombocytopenia is present, ACTH or a corticosteroid may be used to combat the hemorrhage from this cause. Transfusion of whole blood may be beneficial when a specific plasma clotting factor is deficient or absent. As for drug therapy of the disease, objective evidence of improvement will occasionally result from the use of urethane. The erratic results may be due to uncontrollable factors such as 1) toxic reactions which preclude the administration of the drug in adequate dosage over a long period of time, 2) variations in absorption, and 3) in extensive disease, a mass of tumor tissue so great as to render the drug virtually ineffective in its control. Steroids are the only other drugs that have produced an objective response. Besides the effects already noted, a decrease in abnormal globulin components of the serum and a decrease in proteinuria have been observed. The dosage of prednisone is 30 to 50 mg. per day in fractional doses. Urethane and prednisone are used only when the signs and symptoms appear to warrant their administration.

EXCRETION OF MECAMYLAMINE AFTER INTRAVENOUS AND ORAL ADMINISTRATION.
Allanby, K. D., and Trounce, J. R. *Brit. M. J.* **2:** 1219 (Nov. 23) 1957.

In hospitalized hypertensive patients, a hypotensive effect from mecamylamine (Inversine) became apparent approximately thirty minutes after the oral administration of the drug but the maximum effect was not reached until one to two hours thereafter. A smooth and sustained fall in blood pressure thereafter lasted up to twelve or more hours. The duration of effect appeared to be related to the rate of excretion of the substance. Fifty per cent or less of the total amount recovered after a single oral dose appeared in the urine during the first twelve hours after administration. The amount recovered during the first twenty-four hours was 10 to 20 per cent less after oral administration than after intravenous injection. During the next twenty-four hours, this difference increased to 20 to 30 per cent. Total recovery following an oral dose was approximately 65 per cent, and following an intravenous dose between 80 and 98 per cent. The fact that mecamylamine can be recovered from the urine, and the results of daily excretion studies during maintenance therapy, indicate that mecamylamine is consistently and satisfactorily absorbed from the alimentary tract. Urine which is alkaline prevents the excretion of mecamylamine, so that the drug is likely to accumulate and a prolonged fall in blood pressure result. The administration of acetazolamide probably has an effect similar to that of alkalinization of the urine. The characteristics of excretion of mecamylamine should make it possible for this drug to control blood pressure with relatively infrequent oral dosage and without the fluctuation in blood pressure that has made treatment with some other ganglionic-blocking agents unsatisfactory.

TREATMENT OF RENAL FAILURE WITH THE DISPOSABLE ARTIFICIAL KIDNEY. RESULTS IN FIFTY-TWO PATIENTS.
Aoyama, S., and Kolff, W. J. *Am. J. Med.* **23:** 565 (Oct.) 1957.

The coil kidney, which is now commercially available, is a practical and useful device for use in the treatment of uremia. Patients with severe trauma, crushing injury, fulminant infection or intoxication should, it is believed, receive the benefit of dialysis before chemical changes in the blood indicate impending danger. Dialysis every two or three days may be required. In this study, 90 dialyses were performed in 52 patients. Of 29 patients with acute renal failure, 15 recovered and 14 died. Death might have been prevented in 3 instances if dialysis had been applied earlier. Four of those who recovered might have done so without the benefit of dialysis. The other 11 probably could not have survived without it. Of 23 patients with chronic renal failure, 13 improved and 10 died. Little, if any, benefit resulted in patients with uremia complicated by severe or malignant hypertension. Two of 3 patients with polycystic kidneys fared well. Dialysis in 4 patients with chronic pyelonephritis improved the condition in 3 of them. It also improved the condition and urinary output of 1 patient with subacute glomerulonephritis. The duration of improvement after dialysis averaged seven weeks. One patient with prostatic carcinoma and another with polycystic kidneys remained well eight months after dialysis. Twitching, changes in sensorium and vomiting, when present, usually improved. Fever or severe hypertension sometimes prevented improvement. Decreases in blood pressure occurring in some patients during the first hours of dialysis rarely caused concern, and could be corrected by the transfusion of small amounts of blood. Increases in systolic blood pressure of more than 20 mm. Hg occurred in 44 per cent of the dialyses. Five patients, hypotensive before dialysis, were able to maintain a satisfactorily high blood pressure thereafter without the use of pressor agents. The administration of ganglionic-blocking agents became necessary in 4 cases of excessive increases in arterial pressure. Few cardiac irregularities appeared. Hemorrhages due to heparin caused no serious problems. During the dialysis, a dose of 10 mg. of heparin was given per hour; the average dose in adults was 165 mg. The clotting time averaged 16 minutes in the 35 dialyses in which it was determined. A warning is given

against the nasal administration of oxygen and the insertion of other tubes through the nose. In 6 patients with acute renal failure, a slight decrease in urinary output occurred on the day of, or on the day following, dialysis. In 4 patients with chronic uremia, the post-dialysis decrease in urinary output was marked. This decrease appeared to be more likely to take place if there were a decrease in osmolarity of the blood during dialysis of more than 5 mOsm./liter. No hemolysis occurred as a result of dialysis. In patients weighing more than 80 Kg., dialysis of six hours' duration reduced severe uremia to a mild one; in smaller patients, the blood urea might reach normal levels at the end of treatment. The average urea clearance was 105 ml. per minute. The composition of the rinsing fluid was adjusted to correct plasma electrolytes toward normal levels, but sudden adjustments were avoided. The rate of ultrafiltration with the coil kidney approximates 300 ml. per hour of dialysis. It can be increased to 700 ml. Four illustrative case reports are presented. The diagnoses were crush syndrome in 1 patient, anuria following operation in 2 patients, and chronic uremia in 1 patient.

STUDY OF A LONG-ACTING QUINIDINE PREPARATION: EXPERIENCE IN NORMAL SUBJECTS AND IN PATIENTS WITH MYOCARDIAL ABNORMALITY.

Bellet, S.; Finkelstein, D., and Gilmore, H. *A.M.A. Arch. Int. Med.* **100:** 750 (Nov.) 1957.

A study was conducted to determine the plasma levels attained by a long-acting preparation of quinidine gluconate in normal persons and in patients with myocardial disease, and its efficacy in the treatment of cardiac arrhythmias. Following the administration of 1 Gm. of this preparation to 10 normal subjects, the average peak plasma concentration was 4.34 mg. per liter. It was reached at about the end of five hours, was maintained for four to five hours, and decreased gradually thereafter. At twelve and twenty-four hours, respectively, 55 and 25 per cent of the average peak concentration remained. In comparison with the results of other investigators using quinidine sulfate, the peak concentration was higher, the sustained plasma levels persisted longer, and the fall in concentration occurred more gradually. When a second dose of 1 Gm. was given ten hours after the first in 5 normal subjects, the average peak concentration after the first dose was 3.81 mg. per liter and was attained on an average of four hours after the initial dose. Following the second dose, the peak level was somewhat higher and the fall more gradual than after the initial dose. At twenty-four and thirty-six hours after the administration of the first dose, the average plasma quinidine level was 70 and 32 per cent, respectively, of the initial peak concentration. If the drug were to be administered for a long time, it might be that a twelve-hour dosage schedule would prove preferable. When the two-dose per day schedule was employed in 12 patients with myocardial damage and arrhythmias, extrasystoles, atrial tachycardia and atrial fibrillation were abolished at plasma levels similar to those of quinidine sulfate that attained this result. The control of various arrhythmias in 18 additional patients receiving quinidine gluconate are reported in an addendum to this paper. This long-acting preparation is judged worthy of further clinical trial.

THE PRESENT STATUS OF THE TREATMENT FOR MALIGNANCY OF THE STOMACH.

Bowers, R. F. *Am. Surgeon* **23:** 1001 (Nov.) 1957.

Carcinoma, lymphoma and leiomyosarcoma, the common types of gastric malignancy, occur in that order of frequency. Lymphoma offers the best prognosis, with leiomyosarcoma next, and carcinoma the poorest. Only surgery will benefit patients with carcinoma or leiomyosarcoma. Lymphoma is best treated by a combination of radiation and surgery. Large size of the lesion, lack of mobility, and extensive involvement shown radiographically do not necessarily contraindicate surgery. It is contraindicated, however, by distant metastases in such sites as the liver, lung, cervical lymph nodes, and bone and by carcinomatous peritonei and their combinations, except for the presence of a solitary metastatic

nodule in the liver. The summary with regard to surgery states that if the lesion is believed to be malignant after careful appraisal and carrying out the studies referred to (history, physical examination, routine laboratory studies, gastric analysis, radiographic studies, gastroscopy and cytologic examination), and real objective metastatic or extensive findings are not evident, then explore, because it is the patient's only chance for cure, longevity, or short palliative relief. The nature of the lesion must be established by biopsy. Even when a lesion appears not to be resectable, it is essential to establish the presence or absence of lymphoma, because partial resection of this lesion plus immediate radiation therapy will benefit the patient even if the lesion is vicious and extensive. As for operative procedures, partial gastric resection is the procedure of choice when the lesion does not infiltrate the area of the fundus or the cardiac end of the stomach. When more extensive areas are involved, total gastric resection is employed. Involvement of the cardiac end of the stomach and certain extensive lesions in the pars media require inclusion of the lower one-third of the esophagus in the procedure, as well as those parts of the stomach which require removal in order to establish proper margins. Anastomosis by the end-to-end esophagojejunostomy Roux Y procedure has been highly satisfactory and accompanied by fewer complications than esophagoduodenostomy or esophagojejunostomy (end-to-side). Palliative gastroenterostomy has proved unsatisfactory. Feeding jejunostomy may prolong life slightly and afford some comfort, but is used only with full consideration of the personality, philosophy and desires of the patient. In a situation that appears hopeless, the end-result will depend upon the skill of the surgeon in determining the extent of operability and in performing the procedure. The mortality rate for partial gastrectomy has been 2 per cent and for total gastric resection 3.6 per cent. Morbidity occurs in the former cases only when associated conditions such as diseases of the heart, lung or kidney are present. The morbidity rate following total gastric resection for malignancy is decreasing. These procedures provide palliation and enhance longevity and at least temporary cures. Without them, there is no benefit for the patient.

APPENDICITIS IN THE AGED.

Bradley, R. L. *Gastroenterology* **33:** 925 (Dec.) 1957.

Disease of the appendix in elderly persons is likely to be overlooked. In contrast to the fulminating disease in the young, appendicitis in the aged is likely to present vague symptoms of gastro-intestinal distress so that the true nature of the disease process does not become apparent until complications commence. The most potent diagnostic aid is the consideration of appendicitis as a possibility. Acute pathologic conditions in the abdomen in the young alert the physician to the possibility of appendicitis; but in the aged, vascular catastrophes, obstruction of the bowel, diverticulitis and diseases that have come to be identified with age, form the differential diagnosis. The lessened incidence of appendicitis in the aged may be accounted for by the fact that the appendix undergoes fibrosis; the lymphoid hyperplasia present during youth resolves. As secretion diminishes, the likelihood of obstruction and resultant distention of the appendix decreases. That the usual acute symptoms are subjectively minimized by elderly persons is partly due to the stoicism that comes with age. Because older persons may have had previous attacks of appendicitis with spontaneous subsidence, they fail to attach proper significance to a recurrent episode. In such cases, it can happen that bands from the omentum to the appendiceal area may cause a strangulating obstruction with dire consequences. The presence of peptic ulcer and prior abdominal surgery will minimize the likelihood of appendicitis being considered as a possibility. Elderly patients with cerebrovascular accidents and arteriosclerotic dementia are unable to evaluate their symptoms. In them, the disease becomes known only with the onset of complications. In 100 cases of appendiceal disease, 85 patients were below 50 years of age, and 15 above that age. Analysis showed a much higher percentage of patients with complicated appendicitis in the older age group—58.2 per cent as compared with 16.2

per cent among those under age 50. Five case reports illustrate the disease process as seen in the aged.

AN ABNORMALITY IN RENAL FUNCTION RESULTING FROM URINARY TRACT OBSTRUCTION.

Bricker, N. S.; Shwayri, E. I.; Reardan, J. B.; Kellog, D.; Merrill, J. P., and Holmes, J. H. *Am. J. Med.* **23:** 554 (Oct.) 1957.

Observations are described on 4 patients in whom an abnormality in renal function developed in association with mechanical obstruction of the urinary tract. Clinically, the presenting manifestations were those of acute renal failure (complete urinary suppression and symptoms and signs of renal insufficiency). Immediately following relief of the obstruction by appropriate instrumentation, polyuria occurred, varying in duration from several days to three and a half months. The maximum 24-hour urine volumes ranged from 4.5 to 15 liters and the 24-hour sodium excretion from 250 to 1,900 mEq. Renal function studies were conducted during the diuretic phase in all patients, and in 2 patients follow-up studies were performed after subsidence of polyuria. The initial studies revealed impairment of glomerular filtration rate, renal plasma flow, and concentrating ability. The most impressive feature of the nephropathy, however, was the abnormality in salt and water excretion which accounted for the polyuria. Analysis of this abnormality, based on current physiologic interpretations, led to the following conclusions: 1) the diuresis was similar to that seen in normal subjects during experimental osmotic diuresis; 2) the diuresis resulted primarily from the delivery into the urine of an excessively high percentage of the sodium and chloride filtered at the glomerulus; 3) the defect in sodium and chloride excretion could be related to suppression of tubular reabsorption; and 4) the latter was located predominantly in the proximal segment. The inability of the patients to decrease salt and water excretion in response to enforced fluid restriction favors the primacy of the tubular defect in the genesis of the polyuria. However, potentiation of the diuresis in 1 patient by the infusion of an isotonic saline solution suggests that concurrent fluid administration may influence the magnitude of the diuresis. Follow-up studies demonstrated improvement in the majority of parameters examined, indicating that the nephropathy attendant upon urinary retention includes multiple renal functions. Certain of the functional patterns noted in the present patients may also be observed in subjects with advanced Bright's disease and with other renal salt and water wasting syndromes. The possibility has been considered, therefore, that qualitatively similar defects in sodium and chloride excretion may be operative in these states. (From authors' summary.)

CORONARY ARTERY DISEASE. INFLUENCES AFFECTING ITS INCIDENCE IN MALES IN THE SEVENTH DECADE.

Brown, R. G.; Davidson, L. A. G.; McKeown, T., and Whitfield, A. G. W. *Lancet* **2:** 1073 (Nov. 30) 1957.

One thousand and sixty-two men aged 60 to 69 years were interviewed and examined. Those with symptoms or physical signs suggestive of coronary artery disease were referred for full cardiologic investigation, and the diagnosis was confirmed in 89 (8.4 per cent).The prevalence seemed to be unrelated to the mental demands of the men's occupations or to their smoking habits. It was fairly closely related to the physical demands of occupation, being highest for men in sedentary work. The association between prevalence and physical demands of work was most evident among men in professional and related occupations (social classes I and II). When all types of disease were considered together, prevalence was not consistently related to social circumstances, but myocardial infarction seemed to increase in prevalence with a shift from men in unskilled occupations (class V) to those in

professional occupations (class I), whereas manifestations other than infarction were more common in class V than in class I. Arterial pressure was raised in patients with coronary artery disease who had not had an infarction, and lowered in those who had. The observations suggest that the prevalence of manifestations of coronary disease—other than infarction—was approximately doubled for an increase of 15 mm. Hg diastolic, or 30 mm. Hg systolic blood pressure. (From authors' summary.)

DIABETIC RETINOPATHY FOLLOWING TOTAL PANCREATECTOMY.

Burton, T. Y.; Kearns, T. P., and Rynearson, E. H. *Proc. Staff Meet., Mayo Clin.* **32:** 735 (Dec. 25) 1957.

The cause of diabetic retinopathy is unknown. It has sometimes been thought that it might be due to a pancreatic factor other than the lack of insulin. If this were true, then diabetic retinopathy would not be expected to occur in the absence of the pancreas. In none of the reports concerning the 34 instances of total pancreatectomy in the literature is reference made to the development of diabetic retinopathy. Therefore, the case records of the 8 patients who have undergone the operation at the Mayo Clinic were reviewed. Two had been followed long enough to permit observations to be made about the development of diabetic retinopathy. These 2 patients were examined after eleven and ten years, respectively. The first patient has no retinal changes. Laboratory studies showed hyperlipemia. A sister of this patient now has diabetes. The second patient had diabetic retinopathy when she was examined three years after pancreatectomy. This patient had no family history of diabetes. Upon re-examination, chemical findings were nearly normal. This study gives no clue to the pathogenesis of diabetic retinopathy but shows that it can develop in the absence of the pancreas.

ADRENOCORTICAL FUNCTION IN PEPTIC ULCER DISEASE.

Cummins, A. J., and Gompertz, M. L. *Gastroenterology* **33:** 898 (Dec.) 1957.

When the basal levels of 17-hydroxycorticoids present in the blood were determined in 16 patients with active duodenal ulcer and 16 control (non-ulcer) patients, the mean levels were not significantly different. Following adrenocortical stimulation by the intravenous infusion of 25 units of ACTH over a four-hour period in 9 of the patients with ulcer and in 10 control patients, no significant difference could be detected in the blood hormone values determined at the end of the infusion. Neither did the levels in the 2 groups differ when the dose was reduced to 12.5 units of ACTH. The adrenocortical responsiveness, as measured by the eosinophil response to adrenocortical stimulation in the four-hour infusion of ACTH, was essentially the same in patients with and without peptic ulcer. The 24-hour urinary excretion of 17-hydroxycorticoids was determined in 26 control patients, 20 patients with duodenal ulcer, and 9 patients with gastric ulcer. These patients were not the same as those in the previous parts of the study. No variation was apparent in the basal excretion of hormone among the 3 groups. The urinary 17-hydroxycorticoid: creatinine ratios were similar. The rises in corticoid excretion following the administration of ACTH-gel in these 3 groups were also similar. The results of these studies do not exclude an adrenocortical mechanism in the causation of peptic ulcer. They do not, however, support the concept of cortical hyperactivity as a direct etiologic agent in peptic ulcer.

CONTRIBUTIONS OF PSYCHIATRY TO THE INSTITUTIONAL CARE OF AGED AND CHRONICALLY ILL PERSONS.

Goldfarb, A. I. *J. Chron. Dis.* **6:** 483 (Nov.) 1957.

Chronic illness is invariably present among persons in a home for the aged. Psychologic stress and emotional overreaction exacerbate and aggravate such illness. A chronically ill person is likely to dramatize his disease and to use it to manipulate his social environment.

Therefore, the psychiatric aspects cannot be overlooked in the treatment of chronic disease. Case reports are presented which illustrate that the institutional care of aged persons with chronic illness and of elderly persons with unstable behavior was improved through psychiatric care. This consisted mainly of reassurance and support to the patient by means of brief interviews, sometimes even widely spaced and informal. The patient benefited by knowing that he had a powerful ally in the physician. The members of the attending staff were oriented as to the objectives of psychiatric care. The patients' dependency upon others was in this manner put to good use. The morale of the patients and consequently of those around them improved. Psychiatric care helped to relieve mental suffering, improve social behavior, and relieve symptoms of emotional overreaction. Through the efforts of the psychiatrist, it was possible to retain some elderly patients in the home who otherwise would have had to become patients in a mental hospital.

THE EFFECT OF VENESECTION UPON RENAL FUNCTION OF PATIENTS WITH CONGESTIVE HEART FAILURE.

Hammond, J. D. S. *Am. J. M. Sc.* **234:** 185 (Aug.) 1957.

In 10 patients with heart failure, venesection produced no consistent change in the renal circulation or urinary excretion of salt. A sustained decrease in salt excretion without a similar change in glomerular filtration rate was seen in only 1 patient; in the remaining patients renal retention of salt was probably already at the maximum level. This is in marked contrast to the effect of venesection on normal subjects, in whom salt excretion continues to decrease after the renal circulation has started to increase towards its initial level. In the twenty-four hours after venesection, the rate of salt excretion remained very low despite small increases in 4 patients. The beneficial effect of venesection in congestive heart failure cannot, therefore, be attributed to its effect on the renal circulation or the urinary excretion of salt. (From author's summary.)

PRIMARY CARCINOMA OF THE GALLBLADDER.

Marshall, S. F., and O'Donnell, B. *Am. Surgeon* **23:** 1040 (Nov.) 1957.

Primary carcinoma of the gallbladder was found in 71 patients during 6871 primary operations for gallbladder disease—an operative incidence of approximately 1 per cent. The average age of the patients was 60.8 years and the sex ratio of women to men, 3 to 1. Carcinoma of the bile ducts occurred in 81 patients in the same series—an incidence of 1.18 per cent. Approximately half of the 71 patients gave a history of gallbladder disease. Pain was the most constant symptom. Loss of weight occurred in 65 per cent of the patients. Fifty-two per cent had a mass in the right upper quadrant, and 37 patients had jaundice that had been present from one day to six months. When roentgenograms were made, they showed a nonfunctioning gallbladder. In only 1 instance was a probable diagnosis of carcinoma of the gallbladder made. The neoplasm proved to be an adenocarcinoma in 40 patients, carcinoma simplex in 22, and an epidermoid carcinoma or adenoacanthoma in 8. Exploration or biopsy alone was performed in 35 patients. The gallbaldder was removed from 15 who survived an average of seven months. Cholecystostomy was performed in 7 patients, and the common duct was explored and drained in 14 patients. Among those undergoing operation, 16 patients died within one month. The maximal period of survival was eight months. Omitted from this calculation were 2 patients who underwent cholecystectomy, 1 of whom lived for eleven years and died of carcinoma of the colon. Stones were present in 42 patients, and absent in 4. Their presence or absence could not be determined in 23 patients. In the remaining 2 patients, a malignant adenoma was found and cholecystectomy performed. One of these patients fared well for thirty-eight months. This study, and published data on the incidence of gallstones in the age group in which carcinoma of the gallbladder is most common, indicate that carcinoma is five times more common in gallbladders with stones than in those without stones. The association of carcinoma with

stones probably is based upon the metabolic disorders that cause the stones rather than upon their abrasive action. The benign and malignant complications are just as likely to develop in the asymptomatic gallbladder as the symptomatic gallbladder.

STUDY OF THE HEMODYNAMIC EFFECTS OF THE AORTO-CORONARY SINUS GRAFT OPERATION IN PATIENTS WITH CORONARY ARTERY DISEASE.

Moir, T W., and Pritchard, W. H. *Circulation* **16:** 1070 (Dec.) 1957.

A group of patients with coronary artery disease in whom an aorto-coronary sinus graft was surgically created (Beck II, revascularization operation) were studied to determine the functional effects on the cardiovascular system. Preoperatively, mean values for basal cardiac output were within the lower ranges of normal and the average blood volume values were normal. Postoperatively, no circulatory abnormalities were demonstrated in patients in whom the aorto-coronary sinus graft was thrombosed at the time of study. In those patients with patent grafts, hemodynamic changes of an arteriovenous fistula were demonstrated. Cardiac output and work increased, effective systemic flow decreased, peripheral resistance fell, and blood volume became greater. The increase in cardiac output was related to an increase in pulse rate in cases with small shunt flows, and to augmentation of stroke volume when fistulas were of greater magnitude and duration. Elevation of the total blood volume was shown to be related to the presence of cardiac failure and not to the presence of the arteriovenous fistula per se. Cardiac failure developed in some of the patients with a functioning aorto-coronary sinus graft and could be reversed with subsequent surgical obliteration of the shunt. The development of cardiac failure in these patients with pre-existing heart disease could not be entirely related to the volume or duration of shunt flow, but rather seemed dependent on a lack of "myocardial reserve" to withstand the added load of an arteriovenous fistula. Increase in volume of shunt flow was related to duration of the functioning aorto-coronary sinus graft and suggested increased venous collateral flow into the right atrium. (From authors' summary.)

DIE TAGESSCHWANKUNG DER EOSINOPHILENZAHL UND DES INTRAOKULAREN DRUCKES (DAILY FLUCTUATIONS IN EOSINOPHIL COUNT AND INTRAOCULAR PRESSURE).

Radnót, M., and Török, E. *Klin. Monatsbl. Augenheilk.* **130:** 763, 1957; through Ciba Literature Review **2:** 307, 1957.

Since ACTH has been used in the treatment of diseases of the eye, ophthalmologists have been forced in day-to-day practice to take into account physiologic fluctuations in the eosinophil count, which is low in the morning and rises in the afternoon. These daily fluctuations, moreover, make it difficult to evaluate the results of the Thorn test. Clinical studies have shown that these changes in eosinophil count are dependent upon light. Even a small quantity of light is sufficient to provoke morning eosinopenia. The light striking the retina through the clouded lens causes a 40 to 50 per cent decline in the number of eosinophils. Morning eosinopenia is not encountered in blind people, patients with degeneration of the macula lutea, or in healthy blindfolded subjects. There also appears to be a connection between eosinophil count and intraocular pressure. The fluctuations in eosinophil count and intraocular pressure are most probably regulated by the hypothalamus-pituitary system. In an assessment of the changes observed in eosinophil count and intraocular pressure in response to light, account must also be taken of the subject's visual acuity and field of vision, because reactions to the physiologic influences of light depend upon normal retinal function.

ASPIRIN AND DIABETES MELLITUS.

Reid, J.; MacDougall, A. I., and Andrews, M. M. *Brit. M. J.* **2:** 1071 (Nov. 9) 1957.

The disappearance of glycosuria and the return to normal of the fasting blood sugar level in a diabetic patient during the administration of aspirin for the treatment of acute rheumatism led to a reinvestigation of its effect in diabetes mellitus. Doses of 1 to 1.6 Gm. every four hours, but with the omission of one dose in the middle of the night, were given to 7 patients with mild to moderately severe disease for a period of ten days to two weeks. Fasting blood sugar levels were reduced to normal or near normal by the end of this time. Glycosuria was abolished. The blood sugar curves were lower during aspirin administration than they were before or after it, but no decisive effect on glucose tolerance was observed. Ketone excretion levels tested in 2 patients fell to normal, in one precipitously and in the other over the two-week period. One overweight patient lost weight but the other patients did not. However, all patients except 2 lost 1.0 to 2.7 Kg. during the week after aspirin was discontinued. This loss was associated with diuresis. Clinical symptoms, such as thirst, polyuria and pruritus, were relieved by aspirin. Side-effects of the drug, like persistent nausea in 2 patients and intermittent vomiting in 1 of them, disappeared when the dosage of aspirin was reduced. Tinnitus and deafness were annoying but disappeared when aspirin was discontinued. Aspirin increased the metabolic rate in 4 patients in whom this determination was made. It would be premature to recommend the use of aspirin in diabetes mellitus. It might have certain advantages, such as the lack of risk of agranulocytosis and of serious hypoglycemic attacks.

PROGNOSIS OF INTERMITTENT CLAUDICATION.

Richards, R. L. *Brit. M. J.* **2:** 1091 (Nov. 9) 1957.

The study of a selected series of 60 patients, all of whom were followed for at least five years or until death, indicates that the prognosis in intermittent claudication is relatively good. Seventeen patients (28.3 per cent) died during the follow-up period, all except 2 of them from cardiovascular causes. The association of hypertension with occlusive peripheral arterial disease appeared to make the prognosis worse. Sixty per cent of those who died were hypertensive, as compared with 30 per cent of the survivors. The prognosis also appeared to be better if the disease were unilateral when the patient was first seen. In this series, with a few exceptions, the younger the patient when claudication began, the longer its duration before death. Among the 43 survivors, a 39 per cent incidence of angina and 29 abnormal electrocardiograms were found. The total incidence of myocardial infarction, angina of effort, and congestive heart failure was 57 per cent. The implication is that the longer a group of patients with claudication is followed, the more of them will show signs of ischemic heart disease. The association of cerebral vascular disease with peripheral arterial disease apparently has not been studied previously. There were only 6 cerebrovascular accidents (3 fatal) in this series, so the number is too small for conclusions to be drawn. The prognosis with regard to life is better than that for angina pectoris or that for myocardial infarction from which the patient has apparently made a good immediate recovery. There was no evidence that patients who underwent lumbar sympathectomy fared better than those who were treated conservatively. It is concluded that the outlook with regard to the claudication and also the affected limb or limbs is probably better than has been realized. As time goes on, the patient appears to be more likely to be disabled by coronary or cerebrovascular disease than by peripherlal arterial disease. This fact must be considered in planning any surgical treatment in intermittent claudication, such as arterial grafting.

POSTURAL BLOOD PRESSURE CHANGES IN THE ELDERLY.

Rodstein, M., and Zeman, F. D *J. Chron. Dis.* **6:** 581 (Dec.) 1957.

Two-hundred and fifty ambulatory residents of a home for aged persons were given an orthostatic tolerance test (Foley). Several months later the patients were questioned as to the presence of symptoms commonly attributed to orthostatic fall in blood pressure and related characteristics, but without relating this questionnaire to the previous procedure. The

group included 85 males and 165 females whose ages were between 61 and 91 years. The results are summarized as follows: Marked falls in systolic blood pressure (more than 62 mm. Hg) or in diastolic blood pressure (more than 40 mm. Hg) were not found on change from the recumbent to the standing position. In no case did the level on standing fall to below 90 mm. Hg systolic and 54 mm. Hg diastolic. Mild but abnormal falls of the systolic and diastolic blood pressure levels on standing were frequent. A high incidence of marked varicose veins and thrombophlebitis was found in the group with falls of more than 20 mm. in systolic pressure on standing. Symptoms such as weakness, dizziness and headache, commonly attributed to orthostatic variations of the blood pressure, were frequent but had no relation to the occurrence of appreciable falls in blood pressure on standing or to the occurrence of elevated resting blood pressure. Symptoms such as dizziness and headache, commonly attributed to hypertension, were frequent but had no relation to the resting level of the blood pressure. The lack of correlation between the symptoms studied, which are commonly attributed either to hypertension or to orthostatic changes in the blood pressure, and the actual physical findings in this series emphasize the need for caution in the interpretation and explanation of untoward subjective sensations in older patients.

HORMONAL THERAPY IN CANCER OF THE BREAST. XII. THE EFFECT OF ETIOCHOLANOLONE THERAPY ON CLINICAL COURSE AND HORMONAL EXCRETION.

Segaloff, A.; Bowers, C. Y.; Gordon, D. L.; Schlosser, J. V., and Murison, P. J. *Cancer* **10:** 1116 (Nov.–Dec.) 1957.

An aqueous suspension containing 50 mg. per cc. of etiocholanolone was administered in a dosage of 100 mg. intramuscularly three times weekly to 18 patients with advanced mammary carcinoma. During urine collections, the dosage was 50 mg. daily. Four of the patients had osseous lesions only, 8 patients had soft-tissue lesions, and 6 patients had both kinds of lesions. The duration of therapy was 15 to 153 days, with a mean of 41 days. There was no objective regression of the lesions in any patient. A uniform increase in 17-ketosteroid excretion occurred but no other remarkable change in hormonal balance. Etiocholanolone caused untoward local reactions in 7 patients and hyperpyrexia in 8 patients.

HORMONAL THERAPY IN CANCER OF THE BREAST. XI. THE EFFECT OF DEHYDROEPIANDROSTERONE ON CLINICAL COURSE AND HORMONAL EXCRETION.

Segaloff, A.; Gordon, D. L.; Bowers, C. Y.; Schlosser, J. V., and Murison, P. J. *Cancer* **10:** 1114 (Nov.–Dec.) 1957.

Nineteen patients with advanced mammary cancer were treated with an aqueous suspension of dehydroepiandrosterone. The suspension contained 50 mg. per cc. and the dosage was 100 mg. intramuscularly three times weekly except when urine collections were being made. At these times the dosage was reduced to 50 mg. daily to avoid peaks and valleys in excretion due to intermittent therapy. The duration of therapy ranged from 12 to 120 days with a mean of 58 days. The distribution of lesions was as follows: soft-tissue lesions, 9 patients; osseous lesions, 5 patients; both soft-tissue and bone lesions, 5 patients. This substance produced no objective regression in the disease. No local or systemic untoward reactions to dehydroepiandrosterone occurred. The only significant change in hormonal balance was a pronounced increase in 17-ketosteroid excretion.

ANKYLOSING SPONDYLITIS AND CHRONIC INFLAMMATORY LESIONS OF THE INTESTINES.

Steinberg, V. L., and Storey, G. *Brit. M. J.* **2:** 1157 (Nov. 16) 1957.

The literature contains few references to the association of ankylosing spondylitis with ulcerative colitis. Six cases are described. Four of these patients had chronic ulcerative

colitis, 1 had Crohn's disease, and 1 had ulcerative colitis and Crohn's disease as well as ankylosing spondylitis. In each case, the onset of backache followed the beginning of bowel symptoms, usually after a few years, but the diagnosis of ankylosing spondylitis was delayed for several more years. The arthritis was centered primarily in the spine. Other joints were involved, but these manifestations were considered to be secondary phenomena. Because of an incidence of 1 per cent of ulcerative colitis among 399 cases of ankylosing spondylitis admitted to the London Hospital, and an incidence of 1 in 2,000 for ankylosing spondylitis among the general population, this association appears not to be due to chance. References that indicate some association between intestinal disorders and spinal disease are cited. Ankylosing spondylitis may represent a nonspecific reaction to disease of the intestinal tract.

L'EMPLOI DES DÉRIVÉS DE LA CORTISONE À ACTION LOCALE DANS LES ÉPANCHEMENTS SÉREUX DE LA PLÈVRE ET DU PÉRICARDE (THE USE OF DERIVATIVES OF CORTISONE WITH LOCAL ACTION IN EFFUSIONS OF THE PLEURAL CAVITY AND PERICARDIUM).

Villa, L., and Ballabio, C. B. *Méd. et hyg.* **15:** 189, 1957; through Ciba Literature Review **2:** 301, 1957.

In cases of effusion into the pleural cavity or the pericardium, the local injection of hydrocortisone acetate has proved beneficial. The primary indication is rheumatic serositis, and the more recent the disease, the better the results. Further indications include tuberculous serositis, exudates associated with lupus erythematosus, and purulent effusions. For the treatment of purulent effusions, however, hydrocortisone should be combined with antibiotics. Exudates following artificial pneumothorax or mutilating lung operations also respond well as a rule. In cases of pericardial effusion with threatened cardiac tamponade, the response is frequently so striking that the intrapericardial injection of hydrocortisone acetate may be said to exert a life-saving effect. There appear to be no contraindications. Local treatment becomes necessary primarily in cases in which systemic therapy has not produced satisfactory results. In the procedure employed, the pleural cavity is first punctured—except when the effusion is slight—and then a dose of 125 to 250 mg. hydrocortisone acetate is injected. This dose can be repeated daily or every other day. Usually, one or two injections suffice to bring about improvement in the general condition, eliminate fever, and cause rapid regression of the exudate, the composition of which gradually becomes normal. Sometimes six to eight injections are necessary. In cases of pericardial effusion, the procedure is the same, but the dosage is 50 to 125 mg. Other drugs may be given orally or parenterally at the same time.

NEWS AND NOTICES

THE GERONTOLOGICAL SOCIETY, INC.
1958 ANNUAL MEETING

The eleventh annual scientific meeting of the Gerontological Society, Inc., will be held at the Bellevue Stratford Hotel, Philadelphia, Pennsylvania, *November 6, 7 and 8, 1958.*

Abstracts of papers for the program should be submitted to the Program Committee for consideration by *July 1, 1958.* Abstracts should be sent to the sub-chairmen of the section in which the author(s) elect to give their paper.

The sub-chairmen are: *Clinical Medicine*—Dr. Ewald Busse, Duke University Hospital, Durham, North Carolina; *Biology*—Dr. Morris Rockstein, Department of Physiology, New York University, 550 First Avenue, New York 16, N. Y.; *Psychology*—Dr. Ethel Shanas, National Opinion Research Center, 5711 South Woodlawn Avenue, Chicago, Illinois; and *Sociology*—Dr. W. M. Beattie, Jr., Department of Sociology, Washington University, St. Louis, Missouri.

Exact details as to the length of a presentation and its place on the program will be made available by the appropriate sub-chairmen. Scientific and commercial exhibits are scheduled with a series of social functions and a meeting open to the public. Chairman of the Exhibitions Committee is Doctor Leo Gitman, 813 Howard Avenue, Brooklyn 12, New York.

The plan of the meeting is to serve as a particular source of information in each section in addition to general sessions for the comprehensive information of all students of gerontology.

Co-Chairmen

Dr. Warren Andrew,
Bowman Gray School of Medicine,
Winston-Salem, North Carolina

Dr. Joseph T. Freeman,
1530 Locust Street,
Philadelphia 2, Pa.

THE NATIONAL COMMITTEE ON THE AGING

The National Committee on the Aging announces that an explanatory brochure called "The National Committee on the Aging. What it is. What it does" is now available for free distribution.

The Committee, whose headquarters is in New York, is a central national resource for planning, information, consultation and materials in the field of aging.

Those who wish to receive the brochure should write to: David Richards, Director of Public Information, The National Committee on the Aging, National Social Welfare Assembly, 345 East 46th Street, New York 17, N. Y.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

BLOOD PRESSURE SOUNDS AND THEIR MEANINGS. By *John Erskine Malcolm, B.Sc., M.B., Ch.B., F.R.C.S.*, Wing Commander, Royal Air Force. Cloth $2.50. Pp. 93. Charles C Thomas, Publisher, Springfield, Illinois, 1957.

THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE By *John C. Krantz, Jr.*, Professor of Pharmacology, School of Medicine, University of Maryland; Member of the General Committee of Revision of the United States Pharmacopeia, and *C. Jelleff Carr*, Senior Research Pharmacologist, Psychopharmacology Service Center, National Institute of Mental Health, formerly Professor of Pharmacology, School of Pharmacy, Purdue University and Professor of Pharmacology, School of Medicine, University of Maryland. Cloth. $14.00. Pp. 1313; Ed. 4. The Williams & Wilkins Co., Baltimore, Maryland, 1958.

PREVENTIVE MEDICINE FOR THE DOCTOR IN HIS COMMUNITY. By *Hugh Rodman Leavell, M. D., Dr. P. H.*, Professor of Public Health Practice, Head of the Department of Public Health Practice, Harvard School of Public Health, and *E. Gurney Clark, M.D., Dr.P.H.*, Professor of Epidemiology, Head of the Division of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine, Columbia University. Cloth. $10.00. Pp. 689; Ed. 2. Blakiston Division, McGraw-Hill Book Company, Inc. New York, N. Y., 1958.

MODERN SEX LIFE. By *Edwin W. Hirsch, M.D.* Paper, .35¢ Pp. 160. A Signet Book. The New American Library of World Literature, Inc., 501 Madison Avenue, New York 22, N. Y., 1957.

CARDIOVASCULAR REHABILITATION. Edited by *Paul Dudley White, M.D.*, Massachusetts General Hospital, Boston; *Howard A. Rusk, M.D.*, Director, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York; *Bryan Williams, M.D.*, Clinical Instructor in Medicine, Southwestern Medical School, University of Texas, Dallas; and *Philip R. Lee, M.D.*, Department of Internal Medicine, Palo Alto Clinic, Palo Alto, California. Cloth. $6.50. Pp. 155. Blakiston Division, McGraw-Hill Book Company, Inc., New York, N. Y., 1957.

THE RELATION OF PSYCHIATRY TO PHARMACOLOGY. By *Abraham Wikler, M.D.*, National Institute of Mental Health, Addiction Research Center, Department of Health Education, and Welfare, Public Health Service Hospital, Lexington, Kentucky. Paper. $4.00 Pp. 322. The Williams & Wilkins Co., Baltimore, Maryland, 1957.

THE INCURABLE WOUND and Further Narratives of Medical Detection. By *Berton Roueché*. Cloth. $3.50. Pp. 177. Little, Brown & Company, 34 Beacon Street, Boston 6, Massachusetts, 1958.

METHODOLOGY OF THE STUDY OF AGEING—Ciba Foundation Colloquia on Ageing, Volume 3. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Cecilia M. O'Connor, B.Sc.* Cloth. $6.50. Pp. 202. 47 Illustrations. Little, Brown and Company, Boston, Massachusetts, 1957.

HORMONES IN BLOOD—Ciba Foundation Colloquia on Endocrinology, Volume XI. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.* and *Elaine C. P. Millar, A.H.-W.C., A.R.I.C.* Cloth. $9.00. Pp. 416. 74 Illustrations. Little, Brown and Company, Boston, Massachusetts, 1957.

THE NEW FRONTIERS OF AGING. Edited by *Wilma Donahue* and *Clark Tibbitts.* Cloth. $5.00. Pp. 209. The University of Michigan Press, Ann Arbor, Michigan, 1957.

AORTOGRAPHY—Its Application in Urological and Some Other Conditions. By *W. Barr Stirling, CH.M., F.R.C.S. (ED.), F.R.F.P.S.G.*, Senior Assistant, Urological Department, Glasgow Royal Infirmary; Consultant Urologist, Ministry of Pensions. Cloth. Approx. $8.00. Pp. 292. E. & S. Livingstone Ltd., Edinburgh and London, 1957; The Williams & Wilkins Co., Baltimore, Maryland.

THE CLINICAL APPLICATION OF HORMONE ASSAY. By *John A. Loraine, M.B., Ph.D. (Ed.), M.R.C.P. (Ed.)*, Member of Scientific Staff, Clinical Endocrinology Research Unit (Medical Research Council) University of Edinburgh; Associate in Endocrinology, Western General Hospital, Edinburgh, with a Foreword by *J. H. Gaddum, Sc.D., F.R.S.* Professor of Pharmacology and Materia Medica, University of Edinburgh. Cloth. $7.00. Pp. 368. E. & S. Livingstone Ltd., Edinburgh and London, 1958; The Williams & Wilkins Co., Baltimore, exclusive U. S. Agents.

PSYCHOLOGICAL ASPECTS OF AGING. Proceedings of a Conference on Planning Research, Bethesda, Maryland, April 24–27, 1955. *John E. Anderson*, Editor. Paper. $2.00. Pp. 323. American Psychological Association, Inc., 1333 Sixteenth Street N.W., Washington 6, D.C., 1956.

PSYCHOSOMATICS—A SERIES OF FIVE LECTURES. Edited by *Joh. Booij*, Formerly Adjunct-Medical Superintendent of the Psychiatric and Neurological Clinic (Valerius Clinic); Professor and Director of the Neurobiochemical Laboratory, Free University, Amsterdam. Published under the auspices of The Netherlands Society for Psychiatry and Neurology. Cloth. $5.00. Pp. 125. Elsevier Press, Incorporated, Bank of the Southwest Building, Houston 2, Texas, 1957.

Books for review should be sent to Edward Henderson, M.D., Editor-in-Chief, 236 Midland Avenue, Montclair, New Jersey.